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CONGENITAL STEATORRHOEA

By REGINALD MILLER and HERBERT PERKINS

(From Paddington Green Children's Hospital)

In this paper we present a clinical and analytical study of a case of congenital steatorrhoea and compare it with the only previous example of the condition as yet reported. The term steatorrhoea, which has sometimes been used to cover all cases passing an obvious excess of fat in the stools (fatty diarrhoea, diarrhoea alba), is here used in its more correct and restricted sense, namely, as indicating a passage from the bowel of separated liquid fat which congeals on cooling (*Butterstühle*). This phenomenon, which patients may describe as the passage of butter, oil, or grease, is one of comparative rarity.

Acquired steatorrhoea is a well-known symptom. The most clearly defined of such cases are those associated with acquired disease of the pancreas, in which the steatorrhoea is regarded as due to a failure of the action of the pancreatic lipase. Indeed it is generally held, as Salomon has stated (5), that true steatorrhoea is observed only in pancreatic disease. Congenital steatorrhoea, in which the stools are abnormal from birth, has, so far as we know, only been studied in a single case up to the present time. This unique case was reported in 1913 by Garrod and Hurtley (3) under the title of Congenital Family Steatorrhoea. A summary of this case is given in the authors' words before we introduce our present example.

Summary of Previous Case.

A boy, aged 8 years, had been subject from infancy to true steatorrhoea, i. e. the passage from the bowel of liquid fat, which solidified on cooling. He was the second of a family of five children of parents who were first cousins. The fifth child, also a boy, who died at the age of 11 months, was similarly affected from birth.

The boy exhibited no other morbid symptoms, was well grown and nourished, and in no way infantile.

There were no signs of pancreatic disease, unless the steatorrhoea be such. He had never been jaundiced, and cholalic acid could be detected in his faeces. He had no diarrhoea, nor other manifestations of disease of the intestines, and on a diet containing very little fat his stools assumed a normal appearance and consistence.

Analyses of the stools showed that of the fat which he took by the mouth he excreted some 25 per cent. in his stools, and this percentage of loss was maintained when the fat in his diet was doubled. In other words, the percentage wasted was independent of the amount taken.

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On a constant mixed diet, containing 177 grm. of fat, the total fat in the dried faeces, as neutral fats, fatty acids, and soaps, varied but little on either side of 80 per cent.

When the diet was rich in fat, the splitting of fat was conspicuously impaired, and with an intake of 177 grm. the neutral fat in the stools exceeded 60 per cent. of the total fat; but when the fat in the diet was reduced to 92 grm., the ratio of split to unsplit fat in the faeces was not excessive.

Improved saponification was not followed by improved absorption, and it was evident that the impairment of absorption was not dependent upon deficient splitting of fats.

Neither Fel Bovinum, sodium glycocholate, Pankreon, nor Holadin brought about any improvement of utilization of fats. Some of these preparations increased the fat-splitting, but the pancreas preparations, although they had this effect, appeared to aggravate the defect of absorption.

The boy was presumably the subject of a rare inborn error of fat absorption, probably a Mendelian recessive characteristic, but investigations have not showed where this error lies.

Present Case.

Happening to meet with a case of congenital steatorrhoea it was our endeavour to investigate it along the lines followed by Garrod and Hurtley, in order to make a comparison of the two cases. We regret that our results cannot compare with theirs in completeness. This is not merely due to the difficulty in copying such elaborate work as they published, but also to the fact that before we had completed our investigations the child died during a stay at home.

With a view to studying our results so far as we had gone, we discharged the child from hospital on the understanding that he would be presently readmitted to enable us to try the effect on his fat-digestion of various pancreatic and bile preparations. Most unfortunately while at home he died of septic pneumonia following the removal of carious teeth under an anaesthetic. There was no autopsy. The rarity of the case is sufficient, we feel, to make it advisable to report such results as we had obtained. These were concerned only with the estimation of fat-digestion and utilization under various diets containing an estimated amount of fat.

M. O., aged 3 years; male.

In February, 1914, a boy was brought to see one of us at the Out-patient Department of St. Mary's Hospital, the mother stating that he 'passed butter' by the bowel; which statement she reinforced by the production of a bottle containing pale yellow material looking like congealed grease.

History of onset. The mother stated that ever since the second year of the boy's life she had noticed that material like salad oil came with the motion. In view of the previous case she was examined carefully on the question of the first appearance of this peculiarity. She said that she first noticed it as soon as the child was old enough to be 'held out' over a chamber for an action of the bowels. Asked if she thought that the motions had been normal previous to this age, she replied that she was sure they had not been so. For this opinion she gave two reasons: first, that she had noticed that the child's napkins, in infancy, had always been very greasy and difficult to wash, quite

unlike those of her other children; secondly, that the curiously offensive nature of the stools had been present from the first.

The mother was an intelligent and well-educated woman of a class superior to the average out-patient. Her evidence we regard as satisfactory proof of the congenital nature of the steatorrhoea.

Further history from mother. The child's bowels acted about thrice daily, the motion consisting of unformed pale yellow faecal material with the separated 'oil', which was liquid when evacuated, but which solidified at once in cold water. On only three occasions did she remember there being no 'oil' passed, and then for no longer than a couple of days at a time. Often it escaped without any faeces, being passed spontaneously with flatus. The motions and the 'oil' had a very peculiarly offensive smell, unlike the actions of other children. The boy ate well and took an ordinary diet. When he was fed on green vegetables the 'oil' might be tinged green.

Past history. The child had been in no way difficult to rear. He was breast-fed for nine months, then put on Allenbury's Food, and later on ordinary diet. He had never been troubled with sickness, and had had no illnesses of any sort. He had grown normally. He was subject to colds and coughs.

Family history. (Reinvestigated 1920.) The third and youngest child; following a girl (now) aged $16\frac{1}{2}$ and a boy aged $11\frac{1}{2}$ years. In 1915 (a year after the death of the patient at the age of 3) the mother had hysterectomy performed.

There was no consanguinity between the parents. No other cases of steatorrhoea could be traced amongst the relatives. The other children of the marriage were normal.

Condition on admission. The boy did not appear in any way ill. He was of normal height, but his general physique was rather frail. His weight was 26 lb. Although rather thin there was no very notable lack of subcutaneous fat. His complexion was pale. His face suggested the presence of adenoids. These, with enlarged tonsils and very septic carious teeth, were the only physical abnormalities found. His abdomen was not unduly prominent, and nothing abnormal could be detected on examination in the liver, spleen, or pancreas. The urine was normal.

Pancreatic reactions. Microscopical examinations of the stools showed no obvious defect in protein digestion. The urinary diastase test showed no deviation from the normal (=10). Loewi's adrenalin pupil test was negative.

Dietetic investigations. The child was at first put on an ordinary mixed diet, of which the fat was not estimated. On this diet the condition of the stools was as the mother had described, and the occurrence of true steatorrhoea was verified. A sample of the stools on this diet was analysed and was found to contain 52 per cent. of fat in the dried state (see Table V).

Following this, the child was given, for consecutive periods, three different diets, the fat-contents of which were estimated (diets A, B, and C). In the order named these were increasingly rich in fat. No indicator was used to measure the time taken for food to pass through the alimentary tract, but on each occasion the particular diet was given for three full days consecutively before an analysis of the stools was made. On the fourth day the total faeces excreted during a period of twenty-four hours were collected, weighed, and submitted to analysis.

Our results are therefore obtained from a comparison of a known daily intake of fat and a known daily output of fat.

The estimation of the fat in the faeces was made by the Cammidge modification (1) of the Schmidt-Stokes process (see below).

Diets. As already stated the child was given a mixed diet on admission to hospital. The special diets given later are shown in Table I.

Fat-content of special diets. Milk which was certified to contain 3·5 per

cent. of fat was specially provided for these diets by the courtesy of the Walker-Gordon Milk Laboratories. Each diet contained 1 pint (566 c.c.) of this milk. This amount would contain 19·81 grm. of fat.

Dripping was given in weighed quantities. The percentage of fat in it was taken to be 99·68. Thus from this source the diets contained the following amounts of fat: diet A, nil; diet B, 28·24 grm.; diet C, 56·48 grm.

TABLE I. *Composition of Diets.*

	Diet A.	Diet B.	Diet C.
Milk	1 pt.	1 pt.	1 pt.
Dripping	0	1 oz.	2 oz.
Bread	6 oz.	4 oz.	4 oz.
Biscuits	2 oz.	1 oz.	1 oz.
Boiled fish	2 oz.	2 oz.	2 oz.
Potato	2 oz.	2 oz.	2 oz.
Bovril	1 dr.	1 dr.	1 dr.
Orange	1	1	1
FAT	22 GRM.	49·5 GRM.	78 GRM.

Bread was also given in weighed amounts. Estimated as containing 1·27 per cent. of fat, the amounts of fat in the diets from this source were: diet A, 2·16 grm.; diets B and C, 1·44 grm.

The fat-contents of the other constituents of the diets were not estimated. These food-stuffs were all very low in fat, and were, moreover, practically constant in all the diets.

The diets used, therefore, were reckoned as containing the following totals of fat:

Mixed diet: fat-content not estimated.
Diet A: 22 grm. fat taken daily.
Diet B: 49·5 grm. „ „ „
Diet C: 78 grm. „ „ „

Results of Analyses.

The results obtained by the analyses may be most conveniently discussed under the two headings, (1) utilization of fat, and (2) digestion (splitting) of fat.

1. *Utilization of Fat.*

The results obtained are shown in Table II. Considering first the daily totals of fat taken and fat absorbed, it is seen that, within the limits of the amounts given in our diets, the amount absorbed daily increases as the amount taken daily increases. In this respect our case behaved in the same way as did the previous case studied by Garrod and Hurtley.

TABLE II. *Utilization of Fat.*

	TOTALS: daily, in grm.			PERCENTAGES: per 100 grm. fat taken.	
	Fat in Diet.	Fat excreted.	Fat absorbed.	Excreted.	Absorbed.
Diet A	22·0	3·5	18·5	15·9	84·1
Diet B	49·5	16·1	33·4	32·6	67·4
Diet C	78·0	32·8	45·2	42·1	57·9

Secondly, with regard to the percentage wastage of fat (i.e. the amount of fat excreted per 100 grm. fat taken), our figures show that increasing the amount of fat taken increases the percentage wasted. In this respect our case is in marked contrast to the previous one, for Garrod and Hurtley found that their patient always wasted about 25 per cent. of the fat taken, irrespective of the amount of fat in the diet. This interesting point is referred to in the summary at the end of this paper. Mention should here be made of our observation that while taking diet A (low in fat-content), our patient did not pass separated liquid fat: the stools remained unformed, pale, and offensive, but no true steatorrhoea was present. On the richer diets the symptom recurred.

From these results we conclude that, the more the fat taken, the more will be absorbed. But will there be a limit to this? In our case it would seem that a limit might be reached where the percentage wastage of fat is so much higher than the percentage absorption, that the total absorption would begin to fall in amount. On the other hand it is possible, as Spriggs and Leigh (6) suggest, where the patient's general nutrition is good, the percentage wastage of fat might become constant, as was the case throughout in the analyses by Garrod and Hurtley. In either event, however, it is evident that such an excess of fat may be passed on a diet too rich in fat as to produce diarrhoea with loss of nutrition.

2. *Splitting of Fat.*

Our results under this heading are shown in Table III.

TABLE III. *Splitting of Fat.*

	TOTALS: daily in grm.				PERCENTAGES: per 100 grm. fat excreted.		
	Fat in Diet.	Fat excreted.	Neutral Fat excreted.	Split Fat excreted.	Fat in Dried Faeces.	Neutral Fat in Total Fat.	Split Fat in Total Fat.
Diet A	22·0	3·5	0·4	3·1	31·2	10·8	89·2
Diet B	49·5	16·1	5·8	10·3	40·0	35·7	64·3
Diet C	78·0	32·8	7·0	25·8	62·0	21·1	78·9

Considering first the daily totals, our figures show that within the limits of the diets used in our investigations, the amounts of fat excreted in split form increase as the amount of fat in the diet increases. This result is in consonance with the increased absorption of fat following an increased intake of fat which has already been shown to take place. Evidently, therefore, where diets not grossly excessive in fats are in use, the more fat given daily the more is both split and absorbed daily.

Our percentage figures suggest that this increased fat-splitting with increased fat-intake will only hold good within certain limits of fat-intake. As is seen in Table III our percentage figures, although they do not show a progressive diminution in the percentage of fat split per 100 grm. of fat taken, yet the percentage is highest where the intake of fat is lowest.

As the percentage wastage of fat increases with increasing fat-intake, we think it probable that the percentage splitting of fat diminishes progressively

under the same circumstances, and this in spite of the fact that our figure for diet B is rather lower than for diet C. There is some evidence of excessive output throughout the figures for diet B, and it may be that intestinal hurry accounts for what seems likely to be a discrepancy in our figures.

Cause of Defective Absorption of Fat.

As has been already quoted, Garrod and Hurtley concluded that in their case the defective absorption of fat was not dependent upon deficient splitting of fats. Some of the preparations which they administered in their case improved the splitting of fat without improving the absorption. We were not able, as we have explained, to undertake these investigations, but it would appear from our figures on other grounds that the defective absorption is not merely due to deficient splitting of fat.

In Table IV it is seen that as the dietetic fat increases in amount the percentage utilized diminishes, although at the same time the percentage excreted in a split state (per 100 grm. of fat taken) increases.

Except in this point, our investigations do not help in elucidating the cause of the defective absorption of fat.

Method of Fat Estimation.

In the estimation of the fat-content of the faeces the simple method suggested by Cammidge (1) was utilized. This is essentially an adaptation of the Schmidt-Stokes process for the estimation of fat in milk. It is admittedly not so accurate as the usual Soxhlet process, but Cammidge, comparing the results of both methods in controlled cases, finds the margin of error so small as to be negligible for diagnostic work.

The faeces were dried in the usual way. A weighed quantity was evaporated to dryness over a water-bath, absolute alcohol being added from time to time to assist the process. After cooling in a desiccator to constant weight the dried faeces were powdered in a mortar. Two Schmidt-Stokes (A and B) were taken, and into each was carefully introduced 0·5 grm. of the finely-powdered faeces.

Into tube A 10 c.c. of dilute hydrochloric acid were poured; into tube B the same amount of distilled water. Both tubes were heated for 15 minutes in a boiling water-bath. After cooling, the tubes were filled up to the 50 c.c. mark with ether, and after prolonged agitation were put aside for the ether extracts to clear.

From each tube 20 c.c. of the ether extract were withdrawn by a pipette and delivered into weighed beakers. The ether was evaporated and the residues dried to constant weights. These being determined, it is but a simple matter to calculate the total fat in both ether extracts and the percentage of fat in the stool.

The ether extract of tube A, the contents of which had been heated with dilute hydrochloric acid, gives the total fat. The ether extract of tube B, which had been treated with distilled water, gives the sum of the neutral fats and free fatty acids (i. e. the unsoaped fats). The difference between the two gives the combined fatty acids or soaps.

The relation between the neutral fats and the free fatty acids was determined by dissolving the ether extract from tube B in an excess of ether and titrating with decinormal alcoholic soda, using phenolphthalein as an indicator. The number of cubic centimetres used to neutralize the solution, multiplied by

TABLE IV. *Absorption and Splitting of Fat.*

	PERCENTAGE: per 100 grm. fat taken.		
	ABSORBED.	EXCRETED.	
		Split Fat.	Neutral Fat.
Diet A	84·1	14·1	1·8
Diet B	67·4	20·8	11·8
Diet C	57·9	33·1	9·0

TABLE V. *Summary of Analyses.*

	TOTALS: Daily in grm.							PERCENTAGES.					UTILIZATION.	
	Fat in Diet.	Faeces.	Dried Faeces.	Fat excreted.	Neutral Fat.	Fatty Acids as Stearic Acid.	Soap as Stearic Acid.	Fat in Dried Faeces.	Neutral Fat in Total Fat.	Fatty Acid in Total Fat.	Soap in Total Fat.	Split Fat in Total Fat.	Fat excreted per 100 grm. of Fat taken.	Fat absorbed per 100 grm. of Fat taken.
Mixed Diet								52·0	40·6	55·4	4·0	59·4		
Diet A	22·0	32·1	11·2	3·5	0·4	1·9	1·2	31·2	10·8	54·6	34·6	89·2	15·9	84·1
Diet B	49·5	240·0	40·4	16·1	5·8	7·3	3·0	40·0	35·7	45·3	19·0	64·3	32·6	67·4
Diet C	78·0	210·0	53·0	32·8	7·0	18·0	7·8	62·9	21·1	55·0	23·9	78·9	42·1	57·9

0·0248, gives the weight in grammes of free fatty acids contained in the quantity of faeces originally used; and the difference between this and the weight of the ether extract gives the quantity of neutral fat.

Summary and Conclusions.

We have here reported a second example of congenital steatorrhoea and compared it with the only other similar case in the literature, that published by Garrod and Hurtley in 1913. We may now present a summary of the similarities and differences between the two cases.

We enumerate first those points in our case which were similar to those found in the previous case. Our patient was a boy who had passed separated liquid fat since birth, and persisted in doing so except on a diet markedly low in fat-content. Yet this failure in the absorption of fat did not result in any definite stunting of the child's stature by the age of 3 years. Although the power of fat-splitting was somewhat impaired, more especially on diets rich in fat, the failure in fat-utilization did not appear to be merely dependent upon this factor. Unless the true steatorrhoea be regarded as a definitely pancreatic symptom, there was no evidence of pancreatic disease so far as this was tested. The urinary diastase figure was normal, Loewi's pupil test was negative. More particularly, there was found no microscopical evidence of failure in protein digestion. We are not able to say wherein the error responsible for the excessive fat wastage lies. But our case is in line with Garrod's suggestion (2) that there is an 'inborn error of metabolism probably due to the absence of a normal enzyme, presumably a pancreatic enzyme. It is difficult to believe that there is any real disease of the pancreas.'

Passing to the differences between the two cases there are several points to discuss.

(1) In our case no other member of the family was known to be similarly affected, whereas the previous case was the second example in one family. This constitutes, we think, a very superficial point of dissimilarity. Apart from the presumable difficulty in tracing faecal anomalies in ancestors, it is, of course, well recognized that familial diseases very frequently appear sporadically without family incidence. In the previous case, it is noteworthy, the parents of the two children were first cousins. This would undoubtedly have the effect of emphasizing or unmasking any family tendency. In our case there was no such consanguinity between the parents.

(2) In our case fat-splitting was more efficient than in the previous case.

(3) The most notable difference lies in the fat-utilization on diets rich or poor in fat. In the previous case, irrespective of the amount of fat taken, the wastage of fat remained roughly at the same percentage (about 25 per cent. of the fat taken). In our case increasing the fat-intake led to an increased percentage of fat-loss.

It is not at present easy to know what stress to lay upon this point.

In undoubted pancreatic steatorrhoea, Oskar Gross (4) has found in one case a constant percentage of food-fat lost, and in another an increasing percentage of fat-wastage with increasing fat-intake. Spriggs and Leigh (6) in another case obtained an increasing fat-wastage with increased fat-intake. Thus the results in the previous congenital case of steatorrhoea and in the present case have both been obtained in acquired cases of steatorrhoea due to undoubted pancreatic disease.

Spriggs and Leigh (6) have suggested that a constant percentage loss may only hold good where the patient's general nutrition is good; and it is probable that the general nutrition of our case was not, owing to dental and naso-pharyngeal sepsis, at its best and not so good as in the previous case.

In connexion with this particular point of constant percentage loss of food-fat with increasing fat-intake, Garrod has recently written (2): 'It is a remarkable phenomenon and one not easily explained, but upon which future work may throw light.'

In conclusion, we may state that in our opinion the points of dissimilarity which have been discussed above do not form any real differentiation between our present case and the previous (first) example of congenital steatorrhoea.

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THE SOURCE OF THE URIC ACID EXCRETED IN THE URINE AFTER ATOPHAN

By GEORGE GRAHAM

(From the Medical Clinic, St. Bartholomew's Hospital. Director: Sir Archibald Garrod)

THE action of atophan or phenylquinolin on the output of uric acid was first described by Nicolaier and Dohrn (1) in 1908, and since then has been confirmed by all workers, but there has been considerable discussion as to the mechanism by which this increase is brought about and also as to the source of the 'extra' uric acid. Nicolaier and Dohrn thought that it was due to stimulation of nuclear metabolism. Weintraud (2) denied this, as he thought that the atophan exercised a selective action on the kidneys and so removed the uric acid from the kidneys.

The introduction by Folin of a method for estimating the uric acid in the blood has made it possible to get considerable extra information. Folin and Lyman (3) estimated the amount of uric acid in the blood and urine before and after atophan, and found that when atophan was given there was a decrease in the blood uric acid coincident with the increase in the output of uric acid in the urine.

Folin and Lyman concluded from their experiments that 'there was a selective activity on the part of the kidney which must be responsible for the retention of the uric acid', and that 'atophan made the kidneys more permeable for uric acid'. They also concluded that the increased output represents the diminution of uric acid which had previously accumulated in the blood. Fine and Chace (4) and Steinitz (5) have obtained similar results to those of Folin.

Atophan is not the only drug which acts on the kidney in this way. It has been known for thirty years that sodium salicylate caused an increase in the output of uric acid in the urine. More recently Denis (6) found that it acted just as efficiently as atophan did. Fine and Chace (7) thought that it acted better than atophan did. Denis found that aspirin and sodium benzoate acted in a similar way.

The relation between the uric acid in the blood and that excreted in the urine after these drugs confirms the theory that they enable uric acid which has been retained to be excreted in the urine. Folin and Lyman thought that the 'extra' uric acid represented uric acid which had previously accumulated in the blood. The total amount of uric acid in the blood can be

calculated from the data of the percentage amount of uric acid and the volume of the blood. The exact relation of the volume of the blood to the weight of the body is still undecided. Haldane and Lorrain Smith (8) estimate it as $\frac{1}{20}$ of the body weight by means of the carbon monoxide method. Keith, Rowntree, and Geraghty (9), using the vital red method, considered that it formed $\frac{1}{13}$ of the body weight. This figure agrees with the original figures obtained by bleeding animals to death, and is at present considered the more reliable. Assuming that the blood is $\frac{1}{13}$ of the body weight, a man who weighs 65 kilos will have 5,000 grm. of blood. If the uric acid is present in the normal amount, i.e. 1 mg. per cent., the total uric acid is 0·05 grm. If he has gout and has 5 mg. per cent. the total uric acid is 0·25 grm. The extra output of uric acid after atophan was much greater than this in Folin and Lyman's experiments.

In order to get further information as to the source of this 'extra' uric acid I have made three observations on a man with very severe tophaceous gout, who was a patient in the medical clinic at St. Bartholomew's Hospital. He had very large deposits of uric acid in the joints, bones, and tendon sheaths of the hands and feet. Two fingers had been amputated for chronic suppuration, and on admission to hospital he had many discharging sinuses on the hands and feet.

The man ate a purin-free diet and suffered very little inconvenience from it. The uric acid in the urine was estimated by the Hopkins-Folin method; the uric acid in the blood by the Benedict (10) modification of Folin and McCallum's method. Some difficulty was experienced in getting rid of all the protein of the blood, and on two occasions the estimations were lost for this reason. Fine and Chace's (7) modification, which I have used since, is very useful.

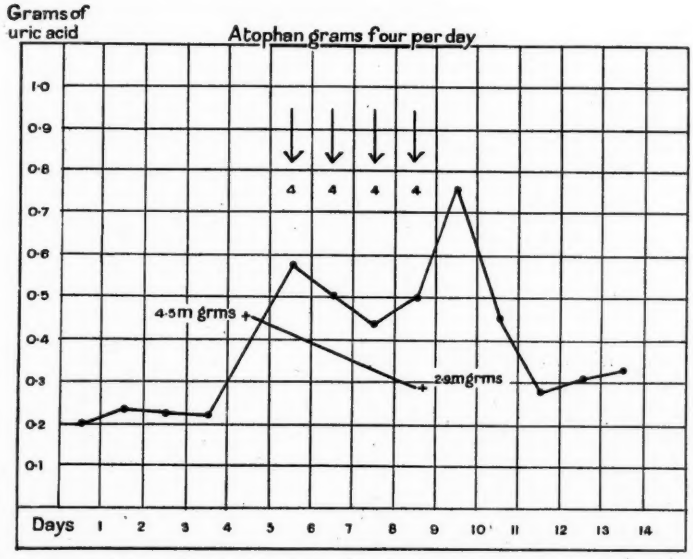

FIG. 1 represents the effect of atophan. The abscissae represent the days of the experiment. The ordinates represent the grm. of uric acid. The uric acid excreted in the urine is represented by ●, the uric acid in the blood in mg. per cent. by +. The atophan was given at ↓.

Experiment I. November, 1919. Weight 51·5 kilos.

The output of uric acid was very low, 0·21 grm. per day. The atophan was given on the fifth day and produced a great increase in the output of uric acid. The uric acid of the blood was determined on the day before the atophan was given and about 10 a.m. of the fourth atophan day. In making calculations of the 'extra' uric acid excreted during the experiment the uric acid excreted on the day on which the uric acid of the blood was determined has been neglected, as the blood was always collected in the first four or five hours of that day.

TABLE I. *Experiment I.*

Day.	Uric Acid in Urine. Grm.	Uric Acid in Blood. Mg. per cent.	Atophan. Grm.	Uric Acid in Urine. Average per Day. Grm.	'Extra' Uric Acid excreted in 3 Days. Grm.
1	0·20	—	—		
2	0·22	—	—	0·22	
3	0·23	—	—		
4	0·22	—	—		
5	—	4·5	—		
6	0·56	—	4		
7	0·50	—	4	0·50	0·84
8	0·44	—	4		
9	0·50	2·9	4		
10	0·75	—	—	0·57	1·06
11	0·46	—	—		
12	0·48	—	—		
13	0·28	—	—	0·34	0·36
14	0·30	—	—		
15	0·32	—	—		

Day.	Volume of Blood. c.c.	Uric Acid in Blood. Per cent. mg.	Uric Acid in Blood. Total grm.
5	4000	4·5	0·18
9	4000	2·9	0·116
			−0·064 Loss

The extra uric acid excreted in three days was 0·84 grm., and during the fourth atophan day and the succeeding two days a further 1·06 grm. of extra uric acid was excreted. After that day the excretion fell to 0·30 grm., a figure which is above the original output.

The uric acid in the blood was 4·5 mg. per cent. on the day preceding the atophan period and 2·9 mg. on the fourth atophan day. The calculation of the total uric acid of the blood shows that it decreased from 0·18 grm. to 0·116 grm., i.e. 0·064 grm., whereas the extra uric acid excreted in the urine in these three days was 0·84 grm. or more than ten times as much.

Experiment II. February, 1920.

The man's general condition had greatly improved, but he still had several sinuses which discharged small masses of urate. The daily excretion of uric acid was much higher and rather irregular. The average output in the preliminary period is therefore rather artificial, as the greatest output was 0·55 grm. and the lowest 0·35 grm.

The blood was collected on the third atophan day and the 'extra' uric acid is estimated for two days. In these two days the extra output was 0·60 grm., with a further output of 0·26 grm. in the next two days.

The total uric acid in the blood decreased from 0·24 to 0·13 grm., i.e. 0·11 grm. This is about $\frac{1}{6}$ of the extra output in the urine.

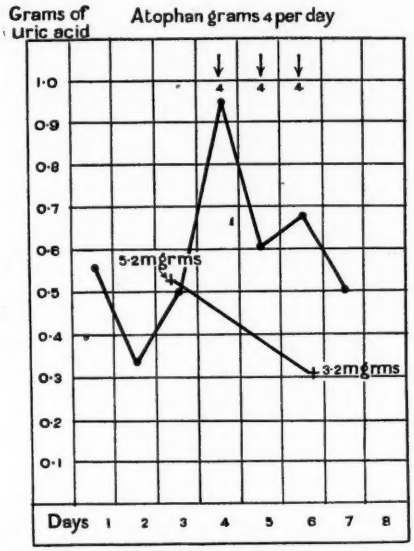

FIG. 2. The abscissae represent the days of the experiment. The ordinates represent the grm. of uric acid. The uric acid excreted in the urine is shown by ●, the uric acid in the blood in mg. per cent. by +. The atophan was given at ↓.

TABLE II. *Experiment II.*

Day.	Uric Acid in Urine. Grm.	Uric Acid in Blood. Mg. per cent.	Atophan. Grm.	Uric Acid in Urine. Average per Day. Grm.	'Extra' Uric Acid excreted in 2 Days. Grm.
1	0·56	—	—		
2	0·33	—	—	0·46	
3	0·50	5·2	—		
4	0·96	—	4		
5	0·60	—	4	0·78	0·64
6	0·68	3·2	4		
7	0·50	—	—	0·59	0·26

Day.	Volume of Blood. c.c.	Uric Acid in Blood. Per cent. mg.	Uric Acid in Blood. Total grm.
3	4150	5·2	0·24
6	4150	3·2	0·13
			−0·11 Loss

Experiment III. In the two weeks before this experiment was performed, 1 grm. of atophan was given four times a day for two days of each week. The general condition of the sinus was very much better and the sinuses were nearly all healed. The uric acid output was more irregular than it had been, varying from 0·50 to 0·80 grm. and back again to 0·50 grm., and for purposes of calculating the extra output I have taken the average output as 0·50 grm., which is that of a healthy man on a purin-free diet. The blood was drawn on the fourth atophan day and at 10 a.m., four hours after the last dose of atophan. The extra output of uric acid in three days was 0·60 grm., and in the next three days there was a retention of 0·15 grm. The figure for the blood uric acid in the preliminary period was lost,

but the blood was collected four days after the last dose of atophan, and the total uric acid of the blood had increased from 0·08 to 0·17 grm., an increase of 0·09 grm. Calculations of the total uric acid of the blood from the data in Fine and Chace's experiments before and after atophan agree with these figures.

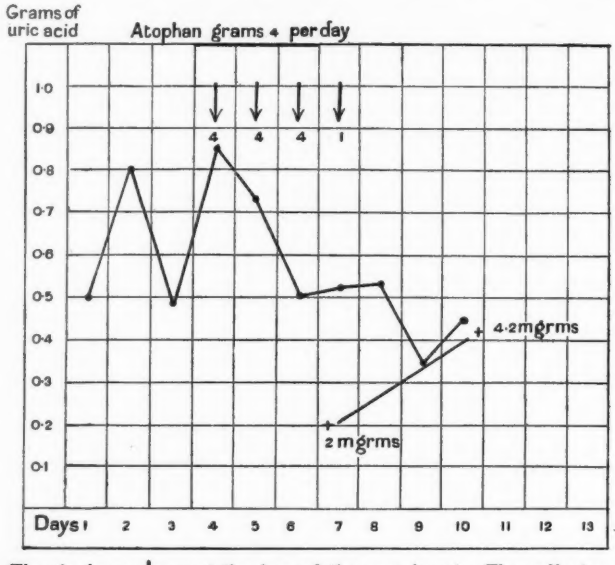

FIG. 3. The abscissae represent the days of the experiment. The ordinates represent the grm. of uric acid. The uric acid excreted in the urine is shown by ●, the uric acid in the blood in mg. per cent. by +. The atophan was given at ↓.

TABLE III. *Experiment III.*

Day.	Uric Acid in Urine. Grm.	Uric Acid in Blood. Mg. per cent.	Atophan. Grm.	Uric Acid in Urine. Average per Day. Grm.	'Extra' Uric Acid excreted in 3 Days. Grm.
1	0·50	—	—	Taken as 0·50	
2	0·80	—	—		
3	0·48	—	—		
4	0·85	—	4	0·69	0·58
5	0·73	—	4		
6	0·50	—	4		
7	0·52	2·0	1	0·48	
8	0·52	—	—		
9	0·35	—	—		
10	0·45	4·2	—		

Day.	Volume of Blood. c.c.	Uric Acid in Blood. Per cent. mg.	Uric Acid in Blood. Total grm.
6	4150	2	0·082
10	4150	4·2	0·174
			+0·092

From these experiments it seems certain that the blood does not contain enough uric acid to supply the 'extra' uric acid even if it were completely emptied of uric acid.

There are two other possible sources for this uric acid: (1) the uric acid held in solution in the tissue fluids of the body; (2) the uric acid deposited in the joints and tissues of the body.

In the case of my patient who has very large deposits of uric acid in his tissues the hypothesis that the deposits are dissolved up is a very tempting one, but the data for the other hypothesis must first be considered.

In 1853 Sir Alfred Garrod (11) showed by means of his thread test that the blister fluid of gouty patients contained uric acid crystals whenever the blood gave the thread test. He also demonstrated the presence of uric acid in the pericardial and ascitic fluids of gouty patients. On one occasion he determined the amount of uric acid in the pericardial fluid of a gouty patient and found that it was 6·9 mg. per cent. These experiments suggest that the uric acid is spread evenly over the water in the body tissues.

In 1913 Fine (12), using the colorimetric method, estimated the uric acid in the tissues of patients who had died of uraemia:

	Mg. per cent.	Mg. per cent.
Blood	15·4	14·3
Pleural fluid	16·7	15·9
Ascitic fluid	18·0	—
Pericardial fluid	—	14·3
Spinal fluid	2·8	2·0
Oedema fluid	18·0	—
Muscle	8·0	3·9
Heart	10·0	7·3
Liver	18·0	15·6
Spleen	12·6	14·3

In 1916 Wells (13), who worked on the tissues of a man who had died after suppression of urine of nine days' duration, showed that there was a great retention of the uric acid in all the tissues.

The amounts of uric acid in the blood in these experiments on renal patients are much higher than those found in gouty patients, but it seems fairly certain that whenever the amount of uric acid is increased in the blood, all the tissues of the body, except the cerebro-spinal fluid, will carry more uric acid in solution.

The water of the body constitutes 90 per cent. of its weight, and if this held the same percentage amount of uric acid in solution as the blood did there would be a large amount of uric acid in the body. I have therefore calculated the amount of uric acid which could be present in the body before and after the atophan.

In Experiment I the uric acid in the body fluids was 2·1 grm. before and 1·36 grm. after the atophan, i.e. a diminution of 0·75 grm. The extra excretion in the urine in the three days was 0·84 grm. In Experiment II the body fluids contained 2·5 grm. before and 1·5 grm. after the atophan, i.e. a diminution of 1·0 grm. The 'extra' uric acid excreted in the urine was only 0·61 grm. Therefore, in Experiment I, which lasted three days, the decrease in the total uric acid of the body approximates to the amount of extra uric acid excreted in the urine. In Experiment II, which only lasted two days, the decrease in the total uric acid of the body is greater than the 'extra' uric acid excreted in the urine.

Fine and Chace (4) mention in a foot-note that calculations from the data of their experiments show close agreement between the uric acid lost from the body fluids and that excreted in the urine. Too much emphasis must not be laid on these calculations, as they may be inaccurate for several reasons: (1) The calculations of the uric acid in the body are made from the data of the percentage amount of uric acid in the blood. This may be correct before the atophan is given, but it is certainly open to error afterwards, as the uric acid in blood then decreases rapidly.

TABLE IV.

Day.	Volume of Water in Body in c.c.	Uric Acid.		'Extra' excreted in Urine in 3 Days. Grm.
		Percentage in Blood. Mg.	Total in the Body. Grm.	
Experiment I.				
4	47000	4·5	2·11	
Atophan				
9	47000	2·9	1·36	
			−0·75	0·84
Experiment II.				
3	47500	5·2	2·5	in 2 days
Atophan				
6	47500	3·2	1·5	
			−1·0	0·63
Experiment III.				
Atophan				
6	47500	2·0	0·94	
10	47500	4·2	2·0	
			+1·06	

Fine and Chace (4) showed that the uric acid of the blood reached its lowest level within twenty-four hours and did not decrease afterwards. Steinitz (5) could detect the decrease two and a half hours after the dose, and it was well marked after five hours. If the uric acid in the blood is much decreased after the atophan there would be a flow of uric acid from the body fluids to the blood. The rate at which this process takes place and the time necessary for equilibrium between the blood and tissue fluid to be established are quite unknown. But the difference between Experiment I and II, which only lasted two days, suggests that the equilibrium may be established after three days.

In the light of this evidence the figures for the total uric acid of the body after the first dose of atophan must be regarded as only approximations. These calculations do suggest that there is a sufficient amount of uric acid in solution in the tissue fluids of the body to supply all the 'extra' uric acid excreted in the urine.

Further, the failure of the atophan to maintain the excretion of the uric acid at the high level may be due to the decrease of the uric acid dissolved in the tissue fluids. If this is the case there is no need to consider the uric acid already deposited in the tissues as the source of the uric acid. But there is one piece of

evidence which suggests that this does play some part in the process. In Experiment III the blood uric acid was estimated three days after the last dose of atophan and had increased from 2·0 mg., to 4·2 mg. and the total uric acid from 1·5 grm. to 2·5 grm., an increase of 1 grm. During this period the uric acid retained was 0·15 grm. below the average output, and yet the uric acid of the body fluid had apparently risen 1·0 grm.

In the experiments of Fine and Chace (4) the uric acid of the blood had returned to about the original level twenty-four hours after the last dose of atophan. The uric acid which accumulated in the blood so rapidly may be uric acid which was picked up from the uric acid already deposited in the tissues. There is, at present, no other evidence which suggests that this takes place, but it is a possibility which cannot be excluded, as tophi sometimes decrease in size.

The part which uric acid plays in the causation of gout is still uncertain. Some workers now regard it as of little importance, but although it may not be the sole cause it is undoubtedly a very important one. It is certainly undesirable for a man to carry an excess of such insoluble substance as uric acid in his blood and tissues if he has once had an attack of gout. This accumulation of uric acid in the blood and tissue fluids can be prevented to a large extent by the use of atophan, aspirin, sodium salicylate, or sodium benzoate. As these drugs only cause an increased output of uric acid for two to three days, a period which corresponds with the time in which the blood and body is emptied of the uric acid dissolved in it, it is of no use to give these drugs for long periods. The plan of giving them for two to three days in each week or fortnight seems a suitable one and does not seem to cause any inconvenience to the patient. Steinitz (5) states that it still produces good effects after two years. In this way it seems possible to prevent any great accumulation in the body and so ward off attacks of gout.

Conclusions.

(1) The 'extra' uric acid excreted in the urine after atophan cannot come solely from the *blood*, as the total amount of uric acid in the blood is much too small.

(2) If the water of the body tissues contains uric acid in the same percentage amount as the blood there is sufficient uric acid in the body to supply the 'extra' uric acid.

(3) The evidence that the uric acid already deposited in the tissues can be redissolved is very weak.

(4) Atophan, sodium salicylate, aspirin, or sodium benzoate should be given to gouty people for two or three days of each week.

I wish to express my thanks to Sir Archibald Garrod, the Director of the clinic, for his advice and encouragement.

I also wish to thank the Sister of the ward, Miss N. Powell, for the care with which she supervised the diets and collection of material.

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SOME OBSERVATIONS ON THE BLOOD-SUGAR IN DIABETES

By DENNISON V. PICKERING

Introduction.

We have for some years estimated the blood-sugar frequently in all cases of diabetes treated at Duff House. For the last three years we have made the observations twice a week.

In some cases it looked as though it might be possible to predict the course of the glycosuria in the near future from the amount of sugar in the blood; in other cases the blood-sugar seemed rather to follow the glycosuria; in others, again, there appeared to be little or no relation between the two. I determined, therefore, to investigate the records of a series of cases in order to find out to what extent the behaviour of the blood-sugar affected prognosis; and how it was related to the age of the patient, the duration of the case, its severity, the carbohydrate tolerance, the amount of oxybutyric acid and its derivatives in the urine, and the complications.

Review of Previous Work.

Among the generally accepted facts and views as regards hyperglycaemia and its relation to glycosuria in diabetes the following may be mentioned. There is normally a small amount of sugar in the blood; the figures obtained by different observers, using different methods, vary between 0·04 per cent. and 0·19 per cent.; by Bang's method 0·11 per cent. and 0·16 per cent. have been given as the normal limits (Williams and Humphreys). In diabetes the blood-sugar may be raised; this rise is ascribed to a failure of the liver in storing glycogen followed by a diminution of the power of the tissues to consume. When the hyperglycaemia persists long enough and is sufficiently severe, glycosuria results. The blood-sugar is said to vary directly with the severity of the case, tending to increase as the case progresses. It usually falls to normal or nearly normal during starvation or if the urine is kept sugar-free for a long time without starving.

R. Lépine (1) states that the idea that the blood-sugar is raised in diabetes arises from the fact that observations have always been made on severe cases, and that in reality the blood-sugar is often within normal limits. Allen (2) finds that the blood-sugar is reduced by a diet with low fat-content. He points out the importance of regular estimations of the blood-sugar, and considers that in all cases its reduction to normal should be aimed at. E. I. Spriggs (3) describes the reduction of blood-sugar by fasting and advises regular estimations.

In the last few years a number of investigators have published interesting accounts of the occurrence of hyperglycaemia and glycosuria after feeding with glucose, both in normal patients and in those suffering from certain diseases.

The method was to give a certain amount of glucose, in most cases by the mouth, estimating the sugar in the urine and blood at regular intervals afterwards. After the administration of glucose the blood-sugar gradually rises until a point is reached at which the kidneys allow sugar to pass through into the urine. The height of blood-sugar at which this occurs has been termed the 'renal threshold'. As a result of such experiments C. V. Bailey (4) concludes that the renal threshold is abnormally low in early mild diabetes, and high in diabetes of long standing. G. Graham (6) finds a transient rise in the blood-sugar in a healthy subject (himself) shortly after a meal. In fatigue the rise was greater. He considers that part of the 'extra' sugar is used up immediately by the tissues, the rest being on its way from the liver to the muscles. The greater rise in fatigue he attributes to a slight failure on the part of the muscles in storing glycogen.

Williams and Humphreys (5) find no marked relation in normal persons between the blood-sugar and the length of time which has elapsed since the preceding meal; and in diabetes they find no striking relation between the renal threshold and the duration of the case, although the former shows some tendency to rise as the case progresses. They find that the threshold is lower in younger cases; that before death it may be very high with little or no glycosuria; and that intractable cases have had their carbohydrate tolerance improved by dieting so as to reduce the blood-sugar; that a rising threshold in a case under treatment is a serious sign and that a high threshold in a mild case is probably due to some complication; that a persistently high blood-sugar promotes exhaustion and rapid decline of function, the high renal threshold being a safety measure, that is, a physiological expedient to conserve food material; that in severe cases where low diets are necessary for continuation of life, the high threshold is essential to safeguard the impaired carbohydrate metabolism; that a persistently low blood-sugar is a favourable sign, and a high blood-sugar in a case on low diet an unfavourable sign. Finally, they consider that in treatment it is desirable to keep the blood-sugar as nearly normal as possible even when, on account of the high threshold, it might be possible to give much more carbohydrate without glycosuria; and that diabetes should be controlled on the basis of the blood-sugar rather than by urine tests.

Method of Procedure and Explanation of Tables.

In the appendix (pp. 28 to 56) tables will be found abstracted from the records of fifty cases of diabetes of varying severity. No attempt is made to give a full description of each case, only such points being mentioned as may serve to show the type. Working under Dr. Spriggs I had charge of all these patients. The food left over as well as that served was weighed, so that we had an accurate daily record of what was eaten. The whole of the urine was collected daily and the sugar estimated by a gravimetric method. Acetoacetic acid and acetone were tested for daily, and frequently estimated; in severe cases the β-hydroxybutyric acid and its derivatives were often estimated and then given in terms of beta-hydroxybutyric acid. The term 'ketonuria' is used in this

paper in referring to the presence of β-hydroxybutyric acid, acetoacetic acid, or acetone in the urine. The analyses were all carried out in the Duff House laboratories by Mr. A. J. Leigh or by Mr. A. B. Weir. The blood-sugar was, as a rule, estimated twice a week. The blood was taken between 10 a.m. and 11 a.m. (i. e. 1¼ to 2 hours after breakfast was finished) from a puncture in the finger. The sugar was estimated by Bang's method. The figures are in each case the average of two or three, usually three, estimations. The normal we found to be from 0·11 per cent. to 0·14 per cent. Recently, however, Mr. Leigh found that there was an error of a constant quantity in the results and that, therefore, the figures we had been getting did not represent the actual percentage of sugar in the blood. The height above normal and the variations, however, are correctly shown. We have now discarded Bang's method in favour of MacLean's (7).

The blood-sugar is described as 'high' when it frequently reaches 0·20 per cent. or rises considerably above that amount. In all other cases it is described as 'low', although above normal. It is described as 'persistent' when it is not much reduced after a period of dietetic treatment, otherwise it is described as 'amenable'. The blood-sugar is described as 'varying with' the carbohydrate in the food or with the glycosuria when its variations correspond more closely with the one than with the other. Cases in which the blood-sugar shows no relation to either are not included in either group. Ketonuria is described as 'considerable' when the acetoacetic acid reaches 2 grammes in the day. In a few cases, e.g. No. 945, the ketonuria was more considerable than would appear from the table, being sometimes higher on dates not given. In describing cases as 'severe', 'mild', and 'slight' I have taken into account the clinical condition, the analysis results, and the carbohydrate tolerance. As might be expected those described as 'severe' almost entirely coincide with those which have 'considerable' ketonuria. No. 724, however, is a 'severe case' with 'slight' ketonuria, and Nos. 737 and 868 are 'mild' cases with 'considerable' ketonuria. Cases are described as long standing when glycosuria was known to exist two years before admission.

It must be noted that the renal threshold in these cases is arrived at in a different manner from that used in the experiments described above in which glucose was given by the mouth, the glycosuria and hyperglycaemia being estimated at numerous short intervals afterwards. In this paper the height of the blood-sugar on any day when sugar appeared in the urine, the previous day's urine having been sugar-free, is taken as the renal threshold. Further, whenever sugar is present in the urine the renal threshold is taken as being below the blood-sugar figure of that day. Again, when there is no glycosuria the renal threshold must be above the blood-sugar. It is evident that the former method gives more accurate results, but if the renal threshold is to be of much clinical value it will have to be arrived at by some simple method such as that adopted in these tables rather than by experiments which could not be carried out in most cases with sufficient frequency.

Analysis of Tables and Deductions.

In analysing the cases I have made a series of tables comparing the age, clinical severity, duration of disease, carbohydrate tolerance (judged by glycosuria) and degree of ketonuria, in turn, with the height of the blood-sugar, its amenity to dietetic treatment, its variation with glycosuria or carbohydrate, and lastly, the renal threshold. The total number of cases at the head of the tables adds up to 51, because on readmission Case No. 761 showed a change of type and therefore appears in more than one class.

I. *Table showing Relation of Age to Blood-sugar and Renal Threshold.*

Age	10–20	20–30	30–40	40–50	50–60	Over 60.
No. of cases	2	4	5	17	13	10
Blood-sugar:						
High	2	3	2	13	7	9
Low	0	1	3	4	6	1
Persistent	1	3	4	13	8	7
Amenable	1	1	1	4	5	3
Varying with glycosuria	2	1	3	7	6	5
Varying with carbohydrate	0	1	2	10	4	4
Renal threshold:						
High	0	3	2	6	1	3
Low	2	1	3	10	11	6
Rising	0	1	0	3	5	0
Falling	0	0	1	0	0	2
Steady	1	0	3	8	3	3
Fluctuating	0	2	1	2	1	2

Observations. There seems to be no constant relation between the age of the patient and the height of the blood-sugar, but above 60 there is a greater proportion of high blood-sugars. No relation is obvious between the age of the patient and the amenity of the blood-sugar to treatment. Age apparently has no effect upon the variation of the blood-sugar with glycosuria or carbohydrate respectively.

Although the only two cases under 20 had a low renal threshold, yet the proportion of low renal thresholds is greater as the age increases. This does not agree with the findings of Williams and Humphreys, but, as explained above, our definition of renal threshold is not the same as theirs.

II. *Table showing Relation of Duration of Disease with Blood-sugar and Renal Threshold.*

	Recent.	Long-standing.
No. of cases	24	27
Blood-sugar:		
High	15	21
Low	9	6
Persistent	17	19
Amenable	7	8
Varying with glycosuria	11	13
Varying with carbohydrate	8	13
Renal threshold:		
High	7	8
Low	16	17
Rising	3	6
Falling	1	2
Steady	9	9
Fluctuating	4	4

Observations. The proportion of high to low blood-sugars is greater among the long-standing cases than among the recent cases.

The proportion of 'persistent' to 'amenable' blood-sugars is the same among recent and long-standing cases.

The proportion of blood-sugars varying with the glycosuria to those varying with the carbohydrate is greater among recent than among long-standing cases.

The proportion of high to low renal thresholds is approximately the same in recent and long-standing cases. In this series of cases the threshold shows no tendency to rise with the duration of the case. In three cases which died the threshold was low. There is no evidence to show whether or not it rose shortly before death.

III. *Table showing Relation of Clinical Severity with Blood-sugar and Renal Threshold.*

	Severe.	Mild.	Slight.
No. of cases	18	27	6
Blood-sugar:			
High	18	17	1
Low	0	10	5
Persistent	14	19	3
Amenable	4	8	3
Varying with glycosuria	12	11	1
Varying with carbohydrate	3	15	2
Renal threshold:			
High	4	11	0
Low	11	16	6
Rising	0	9	0
Falling	1	2	0
Steady	6	8	4
Fluctuating	3	5	0

Observations. The blood-sugar was not entirely within normal limits in a single case, and in most, even of the mild cases, it was frequently above normal. This is in contrast to the findings of Lépine. There are no low blood-sugars among the severe cases and, as might be expected, the proportion of high to low blood-sugars is much greater among the mild than among the slight cases.

Again the proportion of 'persistent' blood-sugars is greatest among the severe and least among the slight cases. Although according to Williams and Humphreys a persistently high blood-sugar might be expected to bring about rapid decline of function, yet in several of these cases the symptoms disappeared and the patients gained steadily in general health and vigour, taking large amounts of carbohydrate, the urine remaining sugar-free. No. 395 is a striking example of such a case.

The proportion of blood-sugars which vary with the glycosuria rather than with the carbohydrate is much the greatest among the severe and least among the slight cases. The explanation of this may be as follows: In a mild case when the blood-sugar is below the renal threshold there will be no glycosuria. On increasing the carbohydrate in the diet the blood-sugar will eventually rise until the renal threshold is reached. When the renal threshold is crossed a little sugar will appear in the urine but the glycosuria will be comparatively negligible, the course of the blood-sugar still corresponding with the carbohydrate in the diet. In a severe case if the threshold rises to protect the carbohydrate metabolism, as suggested by Williams and Humphreys, the relation between the carbohydrate and the blood-sugar will still be close so long as the threshold can rise sufficiently high. But if the threshold remains comparatively low, as in the cases in this paper, a rise in the blood-sugar will be more certainly

followed by a rise in the glycosuria; and small increases of carbohydrate in the food in severe cases have a considerable effect on both blood-sugar and glycosuria. Moreover, in such cases extraneous factors, such as emotions and slight complications (e. g. colds), often have an effect on the blood-sugar and glycosuria. The course of the blood-sugar will therefore correspond more closely with that of the glycosuria.

A greater proportion of high renal thresholds is found among the mild cases.

IV. *Table showing Relation of Carbohydrate Tolerance to Blood-sugar and Renal Threshold.*

	Carbohydrate Tolerance.	
	Good.	Bad.
No. of cases	24	27
Blood-sugar:		
High	12	24
Low	12	3
Persistent	11	25
Amenable	13	2
Varies with glycosuria	7	17
Varies with carbohydrate	13	8
Renal threshold:		
High	7	8
Low	17	16

Observations. As might be expected the proportion of cases with good carbohydrate tolerance was much greater among those with low blood-sugar than among those with high. Again, the proportion of cases with good tolerance was much greater among those whose blood-sugar was amenable to treatment than among the others. Further, it appears that carbohydrate tolerance is more closely associated with the reaction of the blood-sugar to treatment than with its height; for, considering the following table, we see that the ratio of cases with good tolerance to those with bad is greater among those in which the blood-sugar was high and amenable than among those in which it was low and persistent.

	Carbohydrate Tolerance.	
	Good.	Bad.
Blood-sugar:		
Low but persistent	6	3
High but amenable	7	2

In none of the three cases with bad tolerance and 'low' blood-sugar was the latter reduced by treatment.

There are more cases with good tolerance among those with high blood-sugar than one would have expected, but in seven out of the twelve the blood-sugar was reduced by treatment. Of the remaining five all were mild long-standing cases, over 45 years of age, and all but one were stout. In such cases one would expect good carbohydrate tolerance, but not high persistent blood-sugar. An explanation of the latter condition may perhaps be found in the fact that one had albuminuria, one albuminuria and a history of excess in tobacco, and two a history of excess in both tobacco and alcohol. These factors are referred to again in discussing complications.

As might be expected, the number of cases with bad tolerance among those with high and persistent blood-sugar was very great. There was no case with bad tolerance among those with low and amenable blood-sugar.

The fact that there is a much greater proportion of cases in which the blood-

sugar varies with the glycosuria among those with bad tolerance than among those with good agrees with the observation previously made that among the severe cases the blood-sugar tends to vary with the glycosuria.

There was not much difference in the proportion of high to low renal thresholds among the cases with good tolerance and among those with bad.

V. *Table showing Relations of Ketonuria to Blood-sugar and Renal Threshold.*

	Ketonuria Considerable and Persistent.	Ketonuria Considerable, reduced by Treatment.	Ketonuria Slight or Absent.
No. of cases	4	17	30
Blood-sugar:			
High	4	14	18
Low	0	3	12
Persistent	4	12	20
Amenable	0	5	10
Varies with glycosuria	2	11	11
Varies with carbohydrate	2	3	16
Renal threshold:			
High	0	5	10
Low	2	11	20

Observations. Of the cases with considerable and persistent ketonuria, all had high blood-sugar. Among cases with considerable ketonuria, reduced by treatment, the ratio of high blood-sugars to low is nearly 5 to 1; among cases with little or no ketonuria it is $1\frac{1}{2}$ to 1. In other words, cases with considerable ketonuria have as a rule high blood-sugar, especially if the ketonuria resists treatment.

Although the number of cases with high blood-sugar in the 'slight' ketonuria group is large, many of these approximate to the 'considerable' group.

The proportion of cases with considerable to those with slight ketonuria is greater in those with persistent (4 : 5) than in those with amenable (1 : 2) blood-sugars. The cases with persistent ketonuria all have 'persistent' blood-sugar. Among the cases in which the ketonuria is reduced by treatment there is, however, a considerable proportion with 'amenable' blood-sugars.

In accordance with the deductions made from the previous tables the proportion of cases with considerable ketonuria is much greater among those in which the blood-sugar varies with the glycosuria rather than with the carbohydrate. Contrary to expectation the proportion of cases in which the blood-sugar varied more closely with the glycosuria than with the carbohydrate was greater among those cases in which the ketonuria was reduced by treatment than among those in which it was persistent. In these cases there is no clear relation between the height of the renal threshold and the degree of ketonuria.

Complications.

No definite relation could be established between complications and blood-sugar. In Case No. 338 the blood-sugar, which was high, was not further raised on the only occasion on which it was estimated while the patient had broncho-

pneumonia. In Case No. 753, two days after orchitis developed the blood-sugar was higher, although as yet there was no great aggravation of the diabetic condition. Subsequently, however, the latter became rapidly worse and death ensued before another estimation was made.

There were two cases with phthisis; one with a mediastinal growth, one with myocardial degeneration, and one with facial paralysis. They were all mild and showed no striking similarity in blood-sugar. Three cases after moderate doses of bicarbonate of soda had severe oedema, but this did not appear to affect the blood-sugar. In one case the oedema cleared up under treatment, the blood-sugar remaining unaltered.

The following facts, however, are striking. Of nineteen cases with albuminuria sixteen had high blood-sugar. Of eighteen cases with a history of heavy consumption of tobacco fourteen had high blood-sugar. Of eight cases with a history of heavy consumption of alcohol all had high blood-sugar.

General Remarks.

The following observations are derived from a general study of the cases. None of the cases conform to the type known as renal diabetes. Nos. 563, 584, 621, and 885 are the mildest cases, but all have blood-sugar definitely above normal at some stage. No. 563 is the slightest, and even in this case the blood-sugar is just above normal on the two last observations; moreover, at the time of the onset it was probably higher. The glycosuria and symptoms disappeared rapidly on stopping hard work. Some of these cases may be of the type described by G. Graham (8) as 'innocent', but one would hesitate to come to such a conclusion without watching them for a longer period.

Continued fasting brought about a gradual reduction in the blood-sugar. The effect of a fast of one day was to reduce the blood-sugar on the following day in most cases; the reduction was greater and more general in the milder cases. This is in accordance with the fact, already mentioned in the analytical tables, that the blood-sugar in the mild cases reacts better to dietetic treatment than in the severe ones. If the height of the blood-sugar and the course of the glycosuria are considered carefully it will be seen that sometimes a rise of blood-sugar is followed by a rise of glycosuria or by a return of glycosuria in a case which is sugar-free. In some cases this happens several times, but in no case is it invariable. Frequently the glycosuria is already increasing when a rise of blood-sugar is discovered; this must obviously be so when the blood-sugar is only taken twice a week while the glycosuria is estimated daily. Sometimes the glycosuria even decreases within 48 hours of a blood-sugar observation which is higher than the previous one. In such a case the blood-sugar may really be falling, having been higher between the two last observations. The blood-sugar does not, therefore, indicate the course of the glycosuria in the succeeding 48 hours with sufficient frequency to form a basis in prescribing the diet from day to day, or to enable one to predict with any certainty the return of glycosuria in a sugar-free case. At the same time if the blood-sugar rises

considerably in a sugar-free patient this should be taken as an indication either to reduce the carbohydrate temporarily or to stop increasing it. An increase of food, other than carbohydrate, often has comparatively little effect upon the blood-sugar. This is seen by noting those occasions in the tables where the increase of calories is out of proportion to the increase of carbohydrate.

In most of the cases there seems to be no relation between the amount of carbohydrate taken at breakfast and the height of the blood-sugar. As the latter was estimated at times varying from 1¼ to 2 hours after the meal, this means that if there was any 'alimentary hyperglycaemia' it had passed off by that time.

Conclusions.

1. The blood-sugar is almost invariably raised in diabetes.

2. It tends to increase with the duration of the disease.

3. It varies directly with the clinical severity, but in mild cases with albuminuria or a history of heavy consumption of alcohol or tobacco it is often high.

4. It is reduced by fasting.

5. Judging by the carbohydrate tolerance the reaction of the blood-sugar to dietetic treatment is of more importance than its height. That is to say, a case with high blood-sugar which is reduced by restriction of carbohydrate will probably show greater carbohydrate tolerance, and therefore will probably do better, than a case with lower blood-sugar which is not affected by diet.

6. A blood-sugar persistently above normal in spite of treatment is not invariably a bad sign, for the blood-sugar does not always fall to normal when the urine is kept sugar-free for a long time. At the same time, of course, it will be advisable to be cautious in increasing the carbohydrate in such cases, and in giving a prognosis.

7. If the course of the blood-sugar be compared with that of the carbohydrate in the food and with that of the glycosuria, it will be found to correspond more closely with the former in mild cases and with the latter in severe.

8. The amount of carbohydrate in a meal taken from 1¼ to 2 hours beforehand appeared to have no effect on the blood-sugar. Apart from fasting or very low diet the amount of food, other than carbohydrate taken on the previous day, frequently had little or no effect on the blood-sugar.

9. A high renal threshold does not appear to be an unfavourable sign.

10. There is no striking relation in the above cases between the renal threshold and the age of the patient, though, apart from the two cases under twenty, there was a rather greater proportion of low thresholds among the older cases.

11. There is no relation in the above cases between the renal threshold and the duration of the case.

12. The severe and slight cases show greater tendency to steadiness of the renal threshold than the intermediate ('mild') ones.

13. More research on the renal threshold, as defined in this paper, would be

necessary before much reliance could be placed upon it in deciding points of treatment or prognosis.

14. A study of the blood-sugar, particularly of its variation under treatment, is of great value in forming an opinion of the nature and probable course of a case.

The foregoing paper was originally written as a thesis for the M.B. degree at Cambridge University. I wish to express my thanks to Dr. Spriggs for valuable help and suggestions in the work of revision.

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APPENDIX.

Note. The first column of carbohydrate figures gives the amount of carbohydrate in the meal preceding the blood-sugar observation. The second one gives the total carbohydrate in the diet on the previous day. The glycosuria figures are those of the preceding day and of the day of the observation; the latter are given to show the course of the glycosuria immediately after the observation. The ketonuria figures are those of the preceding day.

The following signs are used in the tables:

—	figures not known.
tr	trace.
(tr)	faint trace.
+	moderate quantity not estimated.
+ +	large quantity not estimated.
Ac	acetoacetic acid.
Ox	total acid bodies in terms of beta-hydroxybutyric acid.

No. 338. ♂ Aged 24. Admitted March, 1916.

November, 1915, broncho-pneumonia. December, 1915, glycosuria detected.
Complaint on admission. Incomplete recovery of weight lost.
Examination. Small, rather thin. Drowsy. Some dental stumps. B.P. 108.

Date.	Blood-sugar %	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Mar. 13	0·21	117	149	2	16	2689	4 Ac
22	0·20	206	146	2	26	2773	14 ,,
29	0·17	201	204	2	21	2915	6 ,,
Apr. 13	0·17	68	43	1	1	74	13 Ox
17	0·14	14	17	1	4	217	— Ac
27	0·21	56	64	2	12	1733	3 ,,
May 3	0·24	134	154	2	14	1920	2 ,,
9	0·14	130	48	1	14	1908	11 Ox
11	0·17	15	9	1	1	48	1 ,,
13	0·16	3	0	1	1	48	1 ,,
15	0·14	tr	0	1	1	48	tr ,,
17	0·17	0	tr	1	12	490	1 ,,
19	0·20	tr	tr	1	16	452	tr ,,
21	0·16	5	2	1	18	452	tr ,,
23	0·15	0	tr	1	1	48	tr ,,
25	0·18	tr	(tr)	1	18	860	tr ,,
29	0·17	tr	0	1	18	746	tr ,,
31	0·19	tr	(tr)	1	16	883	tr ,,
June 2	0·18	—	tr	1	19	1030	tr ,,
5	0·22	—	48	1	42	1863	tr ,,
7	0·21	13	0	1	5	1109	tr ,,
9	0·19	tr	11	2	11	1272	tr ,,
13	0·19	12	25	2	1	72	tr ,,
15	0·24	18	29	2	17	1887	1 ,,
20	0·17	8	43	2	1	48	tr ,,
22	0·21	24	—	18	30	2402	2 ,,

Complications. March 25, broncho-pneumonia. April 1, recurrence.

Notes. Severe case. Recent. Carbohydrate tolerance poor. Ketonuria considerable; improved under treatment.

Blood-sugar high; not reduced by treatment; corresponded a little more closely with glycosuria than with carbohydrate.

Renal threshold low, fluctuating.

No. 395. ♂ Aged 57. Admitted June, 1916.

1906, run down after hard work; glycosuria detected.

Complaint on admission. 'Gluey' taste. Stiffness of legs.

Examination. Tall, burly man. Teeth in bad condition; pyorrhoea. B. P. 150.

Date.	Blood-sugar %	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
June 9	0·30	—	++	2	—	—	—
13	0·22	64	43	2	48	3028	0
15	0·23	55	26	1	15	2916	tr Ac
19	0·17	0	(tr)	1	1	48	tr ,,
21	0·15	tr	(tr)	1	21	303	tr ,,
23	0·17	0	0	1	4	924	tr ,,
27	0·14	0	0	1	1	216	tr ,,
30	0·16	0	0	2	5	1589	tr ,,
July 4	0·15	0	0	2	3	313	tr ,,
7	0·16	0	0	2	22	2195	tr ,,
11	0·16	0	0	15	1	216	0
14	0·20	0	0	2	49	3417	0
17	0·17	0	0	1	18	3395	(tr) ,,

Year later. July, 1917.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 20	0·18	0	0	13	38	3009	0
24	0·17	0	0	19	59	3232	0
27	0·20	0	0	19	36	2914	0
			Year later.	*September, 1918.*			
Sept. 13	0·15	0	0	19	96	2817	0
17	0·17	0	0	35	117	2339	0
20	0·17	0	0	35	142	2799	0
24	0·17	0	0	42	13	2379	0

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar high; reduced somewhat by treatment; varied with carbohydrate more closely than with glycosuria.

Renal threshold high; rose a little.

No. 422. ♂ Aged 62. Admitted August, 1916.

1909, exposure in Rocky Mountains. Boils. Glycosuria detected. Thirst and frequency.

Complaint on admission. Weakness Shooting pains in thighs. Impaired sensation in soles of feet.

Examination. Florid and stout. Pyorrhoea; breath smelling of acetone. B. P. 150. Heart a little enlarged; short apical systolic bruit. Basal bronchitis. Knee-jerks absent.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Aug. 10	0·27	—	14	2	13	1885	0
16	0·23	5	tr	3	11	1796	0
19	0·15	0	0	2	17	1932	(tr) Ac
21	0·17	—	0	2	21	1898	0
25	0·24	(tr)	tr	17	57	1901	(tr) ,,
29	0·16	0	0	2	51	1696	0
			Year later.	*August, 1917.*			
Aug. 8	0·26	+	tr	13	—	—	0
10	0·20	tr	0	33	52	1996	0
14	0·21	0	0	16	39	1420	0
17	0·26	0	0	20	69	1130	0
21	0·22	0	0	15	95	2016	0
			Year later.	*September, 1918.*			
Sept. 20	0·22	over 11	8	33	—	—	0
24	0·16	tr	tr	33	108	2199	0
27	0·20	0	0	33	112	2387	0
Oct. 4	0·18	tr	(tr)	30	prob. same	prob. same	0
9	0·18	—	—	33	—	48	0

Complications. Occasional traces of albumin.

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar high; a little reduced by treatment; variation doubtful.
Renal threshold high; fluctuating.

No. 508. ♀ Aged 58. Admitted November, 1916.

1891, mild concussion. 1898, boils. 1911, pneumonia. 1914, thirst; glycosuria detected.

Complaint on admission. Occasional excessive thirst and appetite. Occasional hunger pain. Loss of weight. Sensations of buzzing in head sometimes, with sickness and diarrhoea.

Examination. Rather stout; recent loss of flesh. Some dental stumps. Heart enlarged, first sound inaudible. B. P. 170. Knee-jerks absent.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Nov. 4	0·35	193	114	2	—	—	tr Ac
7	0·24	78	40	12	43	1906	4 Ox
10	0·24	45	33	12	50	1507	7 ,,
14	0·19	31	35	20	49	1487	9 ,,
21	0·20	31	20	2	10	1493	6 ,,
24	0·24	36	23	2	50	1737	4 ,,
Dec. 5	0·22	33	43	2	43	1725	1 ,,
8	0·20	22	14	2	12	1497	3 ,,
12	0·24	17	14	12	16	1613	3 ,,
15	0·19	15	6	2	29	1603	2 ,,
			Year later. January, 1919.				
Jan. 17	0·20	58	46	12	37	722	2 Ac
21	0·28	72	67	12	48	2128	2 ,,
24	0·19	39	52	2	10	1910	2 ,,
28	0·26	37	50	2	11	1963	3 ,,
31	0·27	56	50	2	10	2016	3 ,,
Feb. 4	0·20	62	61	2	12	2182	3 ,,
7	0·23	46	50	2	30	2676	3 ,,
11	0·23	52	85	12	34	2523	3 ,,
14	0·22	36	33	2	10	1847	1 ,,
18	0·24	12	20	2	45	2106	1 ,,
21	0·28	8	9	2	58	2387	1 ,,
25	0·33	81	37	2	64	2280	1 ,,
28	0·23	19	29	2	50	2641	1 ,,
Mar. 4	0·30	67	52	2	73	2350	1 ,,
7	0·26	56	47	2	40	2173	1 ,,

Notes. Severe case. Long standing. Carbohydrate tolerance poor, but up to a point addition of carbohydrate seemed to be followed by diminution of glycosuria. Ketonuria considerable; improved with treatment.

Blood-sugar high; not reduced by treatment; showed little correspondence with either glycosuria or carbohydrate at first.

Renal threshold low; steady.

No. 550. ♂ Aged 61. Admitted May, 1917.

1914, shock—tramcar accident. Later loss of weight and polyuria; glycosuria detected. 1916, sugar-free. 1917, several chills; son killed.

Tobacco rather heavy.

Complaint on admission. Irritable cough. Breathlessness.

Examination. Tongue furred; pyorrhoea. B. P. 118. Dyspnoea; diminished voice and breath sounds and whistling rhonchi right base. With X-rays a dark solid mass at right base.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
May 8	0·21	7	10	+2	53	2567	tr Ac
11	0·16	tr	2	2	17	2115	tr ,,
15	0·13	0	0	1	5	648	1 ,,
18	0·17	0	tr	11	15	1131	tr ,,
22	0·17	0	tr	12	21	1418	1 ,,
25	0·16	tr	tr	17	41	1279	1 ,,
29	0·17	tr	tr	12	50	1399	1 ,,

Complications. New growth right mediastinum.

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar not much above normal; reacted moderately to treatment; corresponded very roughly with both carbohydrate and glycosuria; if anything more in agreement with latter.

Renal threshold low; steady.

No. 563. ♂ Aged 36. Admitted May, 1917.

1900, psoriasis. 1904, mild haemoptysis. 1906, appendicitis; appendix removed. 1915, dysentery. 1916, recurrence of psoriasis. February, 1917, thirst, hunger, polyuria; glycosuria detected.

Complaint on admission. Intermittent tiredness. Indigestion. Giddiness on rising suddenly.

Examination. Psoriasis scattered over trunk, limbs, and scalp. Tongue furred. B. P. 115.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
May 14	0·12	0	0	2	150	2800	0
18	0·12	0	0	7	191	2273	0
22	0·14	tr	0	17	30	2059	0
29	0·12	0	0	32	114	1928	0
June 1	0·14	0	0	37	136	2149	0
5	0·11	0	0	40	167	1058	0
8	0·12	0	0	45	195	2809	0
12	0·15	0	0	28	122	2155	0
19	0·15	0	0	28	145	2056	0

Complications. Phthisis earlier; presumably healed.

Notes. Slight case. Recent. Carbohydrate tolerance good. No ketonuria.

Blood-sugar within normal limits most of time, but rose at end; appeared to vary almost conversely with carbohydrate and glycosuria.

Renal threshold low; steady.

No. 567. ♂ Aged 66. Admitted April, 1917.

1871, nervous breakdown. 1874, eczema. 1907, chill; run down; glycosuria and albuminuria detected. 1916, neuritis of right arm; recurrence of eczema.

Complaint on admission. Debility. 'Griping' pains in stomach. Eczema on arms and knees.

Examination. Tongue furred; teeth defective. B. P. 170. Basal bronchitis. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
May 1	0·26	16	21	19	65	1760	0
3	0·25	17	3	2	30	2001	0
8	0·17	0	0	2	12	1814	0
11	0·14	0	0	1	6	777	0
15	0·17	0	0	9	17	883	0
18	0·19	0	0	17	45	1011	0
22	0·19	0	0	24	71	1198	0
26	0·21	0	0	43	103	1402	0
29	0·22	0	8	29	135	1982	0
June 1	0·18	0	0	17	50	1568	0
5	0·20	0	0	24	69	1654	0
8	0·18	0	0	2	47	2110	0
12	0·24	tr	0	24	83	1753	0
15	0·20	0	tr	24	75	1878	0
19	0·22	0	0	17	68	1164	0
22	0·19	tr	tr	2	19	1315	0

Complications. Slight albuminuria.

Notes. Mild case. Long standing. Carbohydrate tolerance good. No ketonuria.

Blood-sugar high; not much reduced by treatment; corresponded more with carbohydrate than with glycosuria.

Renal threshold high, dropped a little.

No. 568. ♂ Aged 60. Admitted May, 1917.

1874, malaria; infrequent recurrences. 1880, concussion. About 1912, noticed loss of weight. 1915, glycosuria detected accidentally.

Tobacco and alcohol excessive.

Complaint on admission. Constipation. Burning sensation in left foot.

Examination. Florid. Tongue dry and rough, furred. Pulse irregular; B. P. 135. Knee-jerks sluggish.

Day.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
May 25	0·18	0	tr	19	87	2218	0
29	0·19	0	0	1	65	2209	0
June 1	0·18	0	0	17	64	1877	0
5	0·19	0	0	38	101	1839	0
8	0·20	0	0	38	129	2470	0
12	0·22	0	0	43	135	2345	0
15	0·12	0	0	1	1	48	0
19	0·20	0	0	26	117	2061	0
22	0·21	0	0	43	179	2604	0
26	0·19	0	0	26	126	2704	0
29	0·16	(tr)	0	26	165	2480	0

Notes. Slight case. Long standing. Carbohydrate tolerance very good. No ketonuria.

Blood-sugar high; not reduced by treatment; variation doubtful.

Renal threshold low.

Between June 22 and 26 there was a faint trace of sugar in the urine once.

No. 578. ♂ Aged 60. Admitted June, 1917.

1903, glycosuria detected; no symptoms then.

Tobacco excessive.

Complaint on admission. Indigestion. Recent constipation. Shooting pains in feet and knees; occasional swelling of knees; cramps; neuritic attacks in arms.

Examination. Teeth deficient. B. P. 130.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
June 12	0·25	tr	12	1	16	1524	0
15	0·20	5	8	2	16	2397	(tr) Ac
19	0·20	tr	tr	2	14	2453	tr ,,
22	0·20	0	0	1	8	1410	(tr) ,,
26	0·19	0	tr	2	21	2513	tr ,,
28	0·19	0	(tr)	2	22	2426	tr ,,
July 3	0·22	(tr)	0	2	20	2594	(tr) ,,
6	0·20	(tr)	(tr)	2	46	2376	(tr) ,,
10	0·21	(tr)	(tr)	2	51	2450	tr ,,

Complications. Faint traces of albumin June 13 to 18 only.

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar high; not much affected by treatment; followed glycosuria more closely than carbohydrate.

Renal threshold low.

No. 584. ♂ Aged 44. Admitted July, 1917.

1915–17, overworked. May, 1917, glycosuria detected; intermittent.

Complaint on admission. Loss of weight. Tiredness. Weakness of legs.

Examination. Thin. B. P. 100.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 4	0·12	0	0	12	40	1590	0
6	0·12	0	0	12	30	1561	0
10	0·15	0	0	12	74	2147	0
13	0·14	0	0	25	94	2320	0
18	0·12	0	0	36	146	2288	0
20	0·16	0	0	34	169	2424	0
24	0·13	0	0	39	222	2883	0
27	0·15	0	0	38	211	2600	0

Complications. Occasional faint traces of albumin.

Notes. Slight case. Recent. Carbohydrate tolerance good. No ketonuria.

Blood-sugar low; persistent; varies with carbohydrate.

Renal threshold low.

No. 586. ♂ Aged 44. Admitted June, 1917.

1911, glycosuria detected on insurance examination.

Heavy tobacco and alcohol consumption.

Complaint on admission. Sciatica six to eight weeks. Loss of weight a year (9 lb.).

Examination. Liver enlarged. B. P. 124.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 3	0·27	29	32	20	58	1583	0
6	0·22	34	5	1	74	1593	0
10	0·16	0	0	1	2	480	(tr) Ac
13	0·14	0	0	1	4	982	(tr) ,,
18	0·14	0	0	2	19	1885	tr ,,
20	0·20	0	0	2	18	2436	tr ,,
24	0·21	0	0	2	79	2745	0
27	0·22	tr	0	2	47	2478	0

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar high; not reduced after treatment; followed carbohydrate more closely than glycosuria.

Renal threshold high, steady.

No. 598. ♂ Aged 56. Admitted August, 1917.

Length of history unknown. Lost 2 stone in recent years. Tired by heavy war work.

Alcohol rather heavy.

Complaint on admission. Tiredness.

Examination. Stout, florid; unhealthy dental stump. Faint apical systolic bruit. B. P. 130. Chronic ulcer left foot (under great toe).

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Aug. 4	0·20	+	68	39	164	2531	0
7	0·21	46	44	41	193	2560	0
10	0·22	33	14	2	46	2130	0

Notes. Mild case. Probably recent. Carbohydrate tolerance so far poor. No ketonuria.

Blood-sugar high; not so far reduced by treatment; rose steadily in spite of steady reduction of carbohydrate and glycosuria.

Renal threshold low.

This case is included, in spite of the short period of observation, as it is one of the few which show a blood-sugar varying conversely with the carbohydrate and glycosuria. Although the differences in the blood-sugar figures were slight there was undoubtedly a rise in each case. In November, 1917, this case was reported free of sugar; the diet in the interval had been a strict one containing 10 to 15 grm. of carbohydrate daily.

No. 603. ♂ Aged 57. Admitted July, 1917.

1902, pleurisy. 1909, influenza; sugar detected; severe onset. 1912, injury to frontal region; relapse of diabetic condition; improved. 1916, symptoms of acidosis; improved. February, 1917, influenza.

Complaint on admission. Loss of weight. Weakness.

Examination. Thin and weak; flushed; skin dry. Tongue large, dirty, and fissured. Myocardial degeneration. B. P. 130.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 11	0·30	—	108	2	16	2548	9 Ox
13	0·35	102	150	2	14	2329	8 ,,
17	0·25	133	50	2	10	1119	21 ,,
20	0·28	91	104	1	11	1215	9 ,,
24	0·26	81	88	1	12	1338	9 ,,
27	0·20	93	133	1	13	1386	7 ,,
Aug. 3	0·28	150	110	10	31	855	7 ,,
7	0·27	118	76	13	71	1225	5 ,,
10	0·23	144	110	1	87	1671	13 ,,

Complications. Myocardial degeneration.

Notes. Severe case. Long standing. Carbohydrate tolerance very bad. Ketonuria considerable; improved.

High blood-sugar; reduced considerably; varied with glycosuria, irrespective of carbohydrate.

Renal threshold low.

Died August 17, 1917.

No. 610. ♂ Aged 66. Admitted August, 1917.

1900, abscess of leg; sudden thirst and polyuria; glycosuria detected.

Self-indulgent and careless about diet.

Alcohol heavy.

Complaint on admission. Pains in shoulders and legs. May, 1917, inability to walk in going from light to dark. Thirst.

Examination. Thin and feeble. Tongue furred; pyorrhoea; breath smelt of acetone. B. P. 135; pulse 100, small; faint systolic bruit at apex. Knee-jerks absent.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Obsetvation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Aug. 11	0·27	+	250	42	187	2690	—
14	0·38	82	88	14	80	2118	1 Ac
17	0·30	76	71	2	15	1869	4 ,,
21	0·28	79	117	22	54	2147	2 ,,
24	0·30	67	60	12	50	2039	2 ,,
28	0·24	73	49	2	51	1949	2 ,,

Notes. Severe case. Long standing. Carbohydrate tolerance poor. Ketonuria considerable.

Blood-sugar high; not much reduced by treatment; corresponded more closely with carbohydrate than with glycosuria.

Renal threshold unknown.

No. 621. ♂ Aged 57. Admitted August, 1917.

Glycosuria discovered 1916; intermittent.

Complaint on admission. Constipation (20 years); rheumatism.

Examination. Pulse irregular. B. P. 144.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Sept. 4	0·21	(tr)	tr	1	26	1930	0
8	0·17	0	(tr)	2	38	1993	0
11	0·15	0	0	2	32	2058	0
15	0·15	0	tr	2	46	2572	0
18	0·14	0	0	2	47	2373	0
			A Year Later.				
Nov. 12	0·17	(tr)	tr	14	83	2511	0
19	0·13	tr	0	2	87	2941	0
23	0·16	(tr)	0	23	77	2801	0

Complications. Occasional faint traces of albumin.

Notes. Very mild case. Recent. Carbohydrate tolerance good. Hardly any ketonuria.

Blood-sugar low on the whole, reduced by treatment; dropped steadily, irrespective of carbohydrate or glycosuria. A year later blood-sugar was somewhat higher with much more carbohydrate.

Renal threshold low, steady.

No. 667. ♂ Aged 39. Admitted November, 1917.

1897, treated for goitre; phthisis discovered. May, 1917, glycosuria detected.

Complaint on admission. Loss of weight. Polyuria. Tiredness.

Examination. Thin. Tongue rough. B. P. 120. Signs of phthisis both apices. Knee-jerks absent.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Nov. 7	0·25	+	57	2	64	2264	(tr) Ac
9	0·20	74	67	2	63	2577	1 ,,
13	0·17	7	0	1	1	48	2 ,,
16	0·19	0	0	1	1	337	tr ,,
20	0·19	0	(tr)	2	5	1200	1 ,,
23	0·17	(tr)	tr	2	15	1560	tr ,,
27	0·22	0	(tr)	2	10	1528	tr ,,
30	0·21	tr	13	10	20	1641	tr ,,
Dec. 7	0·20	5	tr	2	22	1810	(tr) ,,
11	0·20	17	21	2	25	1940	(tr) ,,
14	0·20	19	0	1	11	1274	(tr) ,,

Complications. Phthisis. Albuminuria.

Notes. Mild case. Recent. Carbohydrate tolerance poor. Ketonuria considerable; improved.

Blood-sugar high, not much affected by treatment; corresponded very roughly with glycosuria.

Renal threshold high, steady.

No. 690. ♂ Aged 31. Admitted January, 1918.

1907, glycosuria detected at insurance examination; no symptoms then. December, 1917, loss of weight and felt ill.

Complaint on admission. Loss of weight.

Examination. B.P. 115. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Jan. 5	0·15	+	8	2	37	2178	0
8	0·13	tr	tr	2	17	2297	tr Ac
11	0·12	tr	tr	2	13	2241	1 ,,
15	0·12	0	0	1	2	445	1 ,,
18	0·11	0	0	2	12	1713	tr ,,
22	0·12	tr	0	2	13	2090	tr ,,
25	0·13	tr	tr	2	30	1988	(tr) ,,
29	0·16	(tr)	9	2	58	2014	(tr) ,,
Feb. 1	0·15	0	0	1	29	1759	(tr) ,,
5	0·11	0	(tr)	2	26	1931	(tr) ,,
8	0·13	tr	tr	19	49	2140	(tr) ,,
12	0·12	3	4	10	59	2085	(tr) ,,
15	0·13	0	0	41	56	2253	0
19	0·14	3	tr	41	67	2354	0
22	0·13	(tr)	tr	28	95	2357	0
25	0·13	tr	tr	11	61	2343	0

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar low; normal at end of treatment on increased carbohydrate; followed both carbohydrate and glycosuria very roughly.

Renal threshold low, fluctuating.

No. 706. ♂ Aged 31. Admitted February 1918.

1917, ulcerated lips; thirst.

Tobacco rather heavy.

Complaint on admission. Thirst and dry mouth. Weakness. Cramps and constipation shortly before admission.

Examination. Very thin. Teeth deficient. B.P. 120; pulse irregular.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Feb. 15	0·24	130	141	17	30	2405	26 Ox
19	0·22	20	9	1	1	48	4 ,,
22	0·19	tr	0	1	1	121	5 ,,
25	0·14	0	0	1	2	477	2 ,,
28	0·21	0	tr	1	2	759	2 ,,
Mar. 4	0·17	0	0	1	1	481	tr ,,
8	0·22	19	16	1	3	983	2 ,,
12	0·19	tr	45	1	1	48	1 ,,
15	0·29	41	42	2	9	1441	2 ,,
19	0·18	tr	27	1	1	48	1 ,,
22	0·20	50	42	2	9	1263	2 ,,
26	0·16	15	50	2	1	48	1 ,,
29	0·17	50	45	2	10	1360	2 ,,

Notes. Severe case. Recent. Carbohydrate tolerance poor. Ketonuria considerable; improved.

Blood-sugar high; hardly affected by treatment; varied more closely with glycosuria than with carbohydrate.

Renal threshold high; dropped a little.

No. 709. ♂ Aged 47. Admitted February, 1918.

1915, heat stroke. 1916 (France), polyuria and thirst; glycosuria discovered. Continued active service. 1917, very ill.

Tobacco rather heavy; alcohol less so.

Complaint on admission. Weakness. Loss of weight. Headaches. Constipation.

Examination. Very thin. Teeth deficient; breath smelt of acetone; abdomen distended. B. P. 120. Knee-jerks absent.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Feb. 16	0·34	—	140	22	—	1431	— Ox
19	0·25	53	19	1	1	48	7 ,,
22	0·23	51	50	1	2	342	9 ,,
26	0·23	17	48	1	3	657	3 ,,
Mar. 1	0·22	30	74	2	5	1073	6 ,,
5	0·23	48	90	1	3	539	4 ,,
8	0·27	70	68	1	3	876	14 ,,
12	0·22	48	127	1	6	989	12 ,,
15	0·30	101	81	1	9	1578	24 ,,
19	0·24	64	106	1	3	237	21 ,,
22	0·24	138	120	1	4	583	12 ,,
26	0·21	64	54	1	1	48	7 ,,
29	0·18	34	32	2	7	1008	19 ,,

Complications. General oedema March 4; later severe pain right thigh; oedema persisted there after clearing up elsewhere. Pyrexia and oedema of bases of lungs, dyspnoea. End of March, oedema, swelling, and pain almost disappeared. Three weeks after leaving abscess in right thigh burst, after which sugar was reported to be lower (July, 1918).

Notes. Severe case. Long standing. Poor carbohydrate tolerance. Ketonuria considerable.

Blood-sugar high, not much reduced by treatment; showed very rough correspondence with glycosuria, even less with carbohydrate; lower at end when complications clearing up.

Renal threshold unknown.

No. 712. ♀ Aged 51. Admitted February, 1918.

Several cases of diabetes in family.

Complaint on admission. Thirst. Tiredness. Polyuria. Constipation starting nine months before admission.

Examination. Thin. Cheeks flushed. B. P. 128.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Feb. 12	0·30	—	181	34	132	1852	0 Ac
15	0·33	183	116	22	111	2232	1 ,,
19	0·22	82	61	2	34	2240	2 ,,
22	0·19	65	62	2	13	2036	3 ,,
26	0·15	0	0	1	1	48	2 ,,
Mar. 1	0·16	(tr)	6	1	2	408	2 ,,
5	0·18	(tr)	6	1	2	335	2 ,,
8	0·22	8	16	1	3	976	1 ,,
12	0·22	18	35	2	7	1116	1 ,,
15	0·19	8	22	2	9	1573	1 ,,
19	0·13	0	(tr)	1	1	48	1 ,,
21	0·16	13	24	1	7	961	1 ,,
26	0·15	0	8	1	1	48	1 ,,
29	0·16	11	19	2	11	1796	1 ,,
Apr. 2	0·19	9	11	2	10	1612	1 ,,
5	0·20	5	12	2	13	1827	1 ,,
9	0·17	5	0	1	13	2353	1 ,,

Notes. Rather severe case. Recent. Carbohydrate tolerance poor. Ketonuria considerable; improved.

Blood-sugar high; reduced by treatment; varied more closely with glycosuria than with carbohydrate.

Renal threshold low.

No. 717. ♂ Aged 49. Admitted March, 1918.

1916, dysentery, scurvy, slight jaundice; glycosuria discovered; later violent diarrhoea.

Rather heavy tobacco and alcohol consumption.

Complaint on admission. Loss of weight. Constipation.

Examination. Tongue furred.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Mar. 8	0·28	—	33	17	30	2244	tr Ac
12	0·25	41	34	17	27	1919	tr ,,
15	0·24	26	tr	2	11	1799	tr ,,
19	0·19	2	tr	2	11	1749	tr ,,
22	0·14	tr	0	1	1	192	tr ,,
26	0·16	0	0	1	4	880	tr ,,
29	0·13	0	0	2	10	1398	0
Apr. 2	0·16	0	0	2	22	1742	0
5	0·20	0	tr	22	35	1656	0
9	0·19	tr	0	1	3	710	0
12	0·20	0	tr	2	24	1632	(tr) ,,

Complications. Possibly diabetes following pancreatitis. Slight albuminuria.

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar high; reduced by treatment; varied less closely with glycosuria than with carbohydrate.

Renal threshold low, rising a little.

No. 724. ♂ Aged 62. Admitted February, 1918.

1915, loss of weight; glycosuria detected; put on starvation treatment but not kept sugar-free.

Complaint on admission. Loss of weight. Weakness. Drowsiness. Dry mouth. Constipation.

Examination. Thin. B. P. 110; short soft systolic bruit at apex. Hb. 70 per cent.; red cells 2,250,000.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Feb. 2	0·22	—	33	2	10	1483	0
5	0·24	34	46	2	11	1465	1 Ac
12	0·22	21	31	2	10	1489	1 ,,
15	0·21	25	41	2	10	1609	tr ,,
22	0·20	15	20	2	11	1816	tr ,,
26	0·16	0	0	1	3	440	0
Mar. 1	0·22	9	7	2	10	1474	0
8	0·22	26	38	10	21	1619	0
12	0·22	9	6	2	20	1538	0
14	0·20	25	30	2	30	1624	0
19	0·19	41	(tr)	1	9	1445	(tr) ,,
22	0·19	0	(tr)	2	9	1252	(tr) ,,
29	0·18	17	0	1	9	1496	0
Apr. 2	0·20	17	16	2	9	1515	(tr) ,,
5	0·22	26	31	2	16	1652	0
9	0·23	41	14	2	12	1918	0
12	0·25	40	49	2	9	1380	0
16	0·25	58	68	2	11	1618	(tr) ,,
19	0·17	7	14	2	1	48	(tr) ,,
23	0·23	56	43	2	13	2803	tr ,,

Complications. Slight albuminuria.

Notes. Severe case. Long standing. Carbohydrate tolerance poor. Ketonuria slight.

Blood-sugar high; not reduced by treatment; varied more closely with glycosuria than with carbohydrate.

Renal threshold low, steady.

No. 728. ♂ Aged 42. Admitted March, 1918.

February, 1918, polyuria; glycosuria detected.

Tobacco heavy, moderate alcohol.

Complaint on admission. Weakness. Loss of weight. Polyuria.

Examination. Thin. Tongue furred; teeth deficient. B. P. 110. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Mar. 9	0·25	—	38	17	53	1778	0
12	0·22	61	56	12	53	2158	(tr) Ac
15	0·24	29	40	2	15	2602	0
19	0·21	62	tr	1	16	2569	(tr) ,,
22	0·12	0	0	1	1	192	0
26	0·12	0	0	1	3	804	0
29	0·12	0	0	2	10	1398	0
Apr. 2	0·15	0	0	2	21	1676	0
5	0·16	0	0	19	35	1849	0
9	0·18	0	0	30	50	1833	0
12	0·18	0	0	15	64	2141	0
16	0·17	0	0	1	5	661	0
19	0·17	0	0	14	27	1911	0
23	0·18	0	0	2	45	2105	0
26	0·16	0	tr	2	54	2140	0
30	0·20	0	0	2	14	1017	0
May 3	0·17	0	0	2	21	2618	0

A Year Later.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Mar. 5	0·24	56	64	2	13	2502	1 Ac
7	0·20	79	62	2	14	2230	1 ,,
11	0·15	(tr)	0	1	1	61	1 ,,
14	0·15	(tr)	tr	1	2	416	1 ,,
18	0·18	4	0	1	6	1191	tr ,,
21	0·15	4	13	1	6	1069	tr ,,
25	0·20	18	(tr)	1	9	1570	tr ,,
28	0·16	tr	11	2	10	1708	tr ,,
Apr. 1	0·18	23	0	2	9	1528	(tr) ,,
4	0·21	tr	12	1	11	1592	0

Complications. Slight albuminuria.

Notes. Mild case. Recent. Carbohydrate tolerance good. Ketonuria very slight.

Blood-sugar high; reduced by treatment; corresponded only very roughly with carbohydrate and glycosuria, but more closely with former.

Renal threshold low.

No. 737. ♂ Aged 42. Admitted April, 1918.

Winter, 1916, operation for gall-stones; constipation afterwards. Glycosuria discovered August, 1917; polyuria.

Heavy tobacco consumption.

Complaint on admission. Occasional thirst. Tiredness.

Examination. Spleen and liver a little enlarged. B. P. 110.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Apr. 10	0·27	+	92	22	98	2851	0
12	0·25	92	71	22	98	2336	1 Ac
16	0·23	36	46	2	16	2665	2 ,,
19	0·20	44	36	2	9	2343	1 ,,
23	0·13	0	0	1	1	48	1 ,,
26	0·14	0	0	1	2	46	1 ,,
30	0·15	0	0	2	14	1329	1 ,,
May 3	0·17	0	0	2	16	1804	1 ,,
7	0·22	(tr)	0	2	32	2282	tr ,,
11	0·18	0	0	2	9	1798	(tr) ,,
15	0·23	0	0	2	23	1891	(tr) ,,
18	0·21	0	tr	2	16	2329	(tr) ,,

Complications. Slight albuminuria.

Notes. Mild case. Recent. Poor carbohydrate tolerance. Ketonuria considerable; improved.

Blood-sugar high; not much reduced by treatment; varied more closely with carbohydrate.

Renal threshold high, steady.

No. 742. ♂ Aged 17½. Admitted April, 1918.

Recent acute onset (eight weeks).

Complaint on admission. Thirst. Frequent micturition. Loss of weight and strength. Sleeping badly. Constipation.

Examination. Thin, flushed, tongue furred. Teeth bad. Breath smelt of acetone. Abdomen distended. Short apical systolic bruit. Hb. 90 per cent.; red cells 3,200,000.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Apr. 16	0·24	+ +	83	27	63	2004	(tr) Ac
19	0·25	62	67	2	37	1935	4 ,,
23	0·21	39	35	2	11	1888	3 ,,
26	0·19	49	37	2	11	1129	1 ,,
30	0·23	49	26	2	15	1898	1 ,,
May 3	0·21	61	9	1	11	2073	1 ,,
7	0·14	0	0	1	1	192	tr ,,
10	0·15	0	0	1	27	654	tr ,,
17	0·17	0	0	2	21	2107	(tr) ,,
21	0·21	0	tr	1	50	1937	0
24	0·15	0	0	2	21	1670	0
28	0·17	0	0	2	33	1605	0

Complications. Recent gall-stone operation. Slight albuminuria.

Notes. Severe case. Recent. Good carbohydrate tolerance as far as tested. Ketonuria considerable; improved.

Blood-sugar high; reduced by treatment; varied closely with carbohydrate and glycosuria, but at end followed latter more closely.

Renal threshold low, steady.

No. 753. ♂ Aged 49. Admitted April, 1918.

1912, thirst, frequency of micturition, furred tongue, loss of weight, tired. Tried fasting at home with unsatisfactory results.

Complaint on admission. Dry, furred tongue. Polyuria. Loss of weight and strength.

Examination. Tongue clean. Breath sweet. Artery thickened. B.P. 110.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Apr. 16	0·26	101	124	2	46	2689	3 Ac
19	0·19	109	81	2	16	1427	4 ,,
23	0·21	69	71	11	13	1958	4 ,,
26	0·20	32	96	2	18	1781	4 ,,
30	0·23	37	121	2	19	2078	4 ,,
May 3	0·21	76	48	2	7	2698	4 ,,
7	0·19	17	tr	2	1	48	3 ,,
10	0·19	0	tr	1	1	168	1 ,,
14	0·20	(tr)	0	1	1	318	tr ,,
17	0·20	tr	17	1	3	870	(tr) ,,
21	0·19	tr	21	1	1	48	(tr) ,,
24	0·21	33	28	1	10	1864	(tr) ,,
28	0·19	12	56	2	1	48	tr ,,
31	0·20	67	80	2	12	2091	tr ,,
June 4	0·21	16	36	2	2	96	tr ,,
7	0·21	69	61	2	12	2195	tr ,,
11	0·20	20	83	2	1	48	tr ,,
14	0·23	26	34	2	12	2164	tr ,,

Complications. Occasional faint traces of albumin. Orchitis starting June 12, probably following slight injury, but doubtful.

Notes. Severe case. Long standing. Carbohydrate tolerance bad. Ketonuria considerable; improved by treatment.

Blood-sugar high; not reduced by treatment; did not vary closely with either glycosuria or carbohydrate.

Renal threshold low, steady.

Died five days after last observation; the day before death the acetoacetic acid rose from a trace to three grm.

No. 760. ♂ Aged 60. Admitted May, 1918.

1908, after influenza and trap accident developed increased thirst; glycosuria discovered four months later; oedema in lower limbs, albuminuria.

Complaint on admission. Pains in calves. Sense of weight and burning in epigastrium after food. Constipation. Sleeping badly. Irritability. Weakness.

Examination. Very nervous and excitable. Teeth deficient. Breath offensive. Pulse 90, irregular. B. P. 132. Emphysema.

Sugar in Urine. Grm.

Date.	Blood-sugar %.	Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
May 15	0·32	+	124	44	—	—	0
18	0·21	20	23	2	15	21	0
21	0·19	9	tr	2	13	2230	0
24	0·24	30	14	2	10	1826	0
28	0·21	tr	0	1	9	1560	0
31	0·19	0	32	2	11	1891	0
June 4	0·24	tr	12	2	9	1512	(tr) Ac
7	0·28	13	18	7	51	664	0
11	0·29	42	25	2	27	1725	0
14	0·19	4	tr	2	8	1407	0
21	0·22	11	tr	2	20	1690	0

Complications. Slight albuminuria.

Notes. Mild case. Long standing. Carbohydrate tolerance bad. Ketonuria very slight.

Blood-sugar high; not reduced by treatment; varied with glycosuria rather than with carbohydrate.

Renal threshold low, steady.

No. 761. ♂ Aged 28. Admitted March, 1918.

Served at Mons, Dardanelles, in Egypt, and on the Western Front.

1915, diarrhoea and vomiting. 1918, severe thirst and weakness.

Complaint on admission. Diarrhoea and vomiting. Fainting. Lack of concentration, impaired memory. Thirst. Feebleness and loss of weight.

Examination. Thin. Pulse 48; artery thickened.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Mar. 27	0·17	29	30	2	16	2466	0
29	0·16	6	8	2	15	2320	tr Ac
Apr. 2	0·17	17	0	1	14	2283	1 ,,
5	0·13	0	0	1	2	410	tr ,,
9	0·18	0	0	2	15	1500	tr ,,
12	0·19	tr	0	2	38	1418	(tr) ,,
16	0·21	0	0	7	16	1662	(tr) ,,
19	0·16	0	0	2	43	1716	0
23	0·18	(tr)	tr	2	25	2199	0
26	0·17	0	0	2	7	1183	0
30	0·19	(tr)	0	2	24	1934	0
May 3	0·16	0	0	2	14	2538	0
7	0·21	tr	tr	2	26	2990	0
10	0·17	0	0	1	1	48	0
17	0·19	0	0	2	14	2097	0
21	0·22	tr	tr	2	17	2065	0
24	0·18	tr	tr	2	11	1768	(tr) ,,
28	0·17	0	0	2	12	2129	(tr) ,,
31	0·15	0	0	2	19	2065	0
June 4	0·21	0	0	2	23	1947	0
7	0·14	0	0	2	43	2169	0
10	0·17	0	0	2	50	2092	0
14	0·13	0	0	2	9	1553	0
18	0·19	0	0	2	36	1904	0
			A Year Later.				
Aug. 29	0·29	132	28	2	—	—	+ Ac
Sept. 2	0·30	0	0	1	1	121	tr ,,
5	0·29	0	0	1	3	635	0
9	0·38	10	9	2	9	1327	0
12	0·34	20	9	2	13	1997	0
16	0·30	15	29	2	12	2141	tr ,,
19	0·29	69	64	2	12	2455	+ ,,
23	0·37	21	85	2	14	2816	+ ,,

Complications. Previous jaundice. Slight albuminuria.

Notes. Mild case. Recent. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar low; not reduced by treatment; corresponded only roughly with glycosuria and carbohydrate.

Renal threshold high, rising.

On readmission rather severe case. Carbohydrate tolerance poor. Ketonuria more than before, but still slight. Blood-sugar high; not reduced by treatment; varied with carbohydrate, not glycosuria.

No. 763. ♂ Aged 51. Admitted May, 1918.

Eighteen months before admission 'almost blind'; thirst, frequency of micturition, weakness. April, 1917, glycosuria discovered.

Complaint on admission. Thirst. Constipation. Poor appetite. Heartburn. Weakness; rapid loss of weight.

Examination. Thin. Dry skin. Tongue dry and rough; teeth bad. B. P. 90. Harsh breathing; rhonchi. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
May 21	0·28	+	38	11	—	—	+ Ac
24	0·24	51	151	2	11	2043	4 ,,
28	0·23	14	40	1	2	90	3 ,,
31	0·22	13	tr	1	2	96	1 ,,
June 4	0·23	7	17	1	2	271	1 ,,
7	0·24	25	20	1	3	874	1 ,,
11	0·27	46	56	2	9	1493	2 ,,
14	0·23	15	27	2	9	1534	2 ,,
18	0·31	30	25	2	9	1437	4 ,,
21	0·26	91	23	2	9	1495	2 ,,
25	0·24	85	59	2	11	1387	6 ,,
28	0·25	48	—	2	9	1527	—

Complications. Slight albuminuria.

Notes. Severe case. Recent. Carbohydrate tolerance bad. Ketonuria considerable; improved under treatment.

Blood-sugar high; not reduced by treatment; varied with glycosuria rather than with carbohydrate.

Renal threshold unknown.

No. 765. ♀ Aged 44. Admitted June, 1918.

April, 1915, very nervous, suffering from war worry; had lump removed from breast. Thirst developed, but there was no examination of urine till a year later. Did well on diet and was much relieved.

Complaint on admission. Being easily tired. Bad taste in mouth.

Examination. Nervous. Rather thin. B. P. 116.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
June 7	0·21	17	—	2	13	2213	(tr) Ac
11	0·23	6	tr	2	13	2232	0
14	0·16	0	tr	2	2	442	0
18	0·20	0	0	2	9	1437	0
21	0·20	tr	tr	2	30	1516	0
25	0·22	tr	0	2	11	1401	0
28	0·25	tr	11	22	20	1616	0
July 2	0·25	0	tr	2	18	1693	0

Notes. Mild case. Long standing. Carbohydrate tolerance bad. Ketonuria very slight; disappeared at once under treatment.

Blood-sugar high; not reduced by treatment; varied roughly with carbohydrate.

Renal threshold high, rising.

No. 774. ♂ Aged 49. Admitted June, 1918.

1916, increased thirst. Xmas, 1917, bad cold; fasting treatment; became very thin and nervous.

Complaint on admission. Dry mouth. Slight tiredness. Frequency of micturition. Sleeping badly. Loss of flesh.

Examination. Thin. Teeth deficient; breath sweet; abdomen distended. B. P. 110. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
June 12	0·28	—	112	2	—	—	+ Ac
14	0·23	54	27	1	1	72	2 ,,
18	0·21	0	tr	1	1	192	3 ,,
21	0·21	0	tr	1	2	413	1 ,,
25	0·23	0	0	1	3	825	1 ,,
28	0·23	tr	46	2	6	1256	1 ,,
July 2	0·21	0	tr	1	3	723	tr ,,
5	0·31	34	47	2	9	1355	(tr) ,,
9	0·27	49	33	2	9	1375	(tr) ,,
12	0·21	53	13	1	10	1628	(tr) ,,

Complications. Occasional slight albuminuria.

Notes. Severe case. Long-standing. Carbohydrate tolerance bad. Ketonuria considerable; improved with treatment.

Blood-sugar high; not reduced by treatment; followed glycosuria rather than carbohydrate.

Renal threshold high, steady.

No. 785. ♂ Aged 12½. Admitted July, 1918.

January, 1918, thought to be getting thin, thirst noticed, seemed tired; glycosuria found. On fairly rigid diet looked better and put on weight, but glycosuria increased. Fasting caused weakness and loss of weight.

Complaint on admission. Weakness. Loss of weight.

Examination. Tongue furred; breath sweet. B. P. 110. Knee-jerks absent.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 11	0·21	84	96	23	50	1723	4 Ac
16	0·19	95	50	2	23	1605	6 ,,
19	0·19	60	79	2	10	1573	6 ,,
23	0·23	90	80	2	5	604	15 Ox

Notes. Severe case. Recent. Carbohydrate tolerance bad. Ketonuria considerable; not reduced by treatment.

Blood-sugar high; not reduced by treatment; varied with glycosuria.

Renal threshold low.

Patient died on July 24.

No. 810. ♂ Aged 32. Admitted August, 1918.

September, 1917, subject to anxiety, noticed tiredness and thirst. January, 1910, glycosuria found.

Complaint on admission. Loss of weight. Tiredness. Constipation.

Examination. Pale. Thin. Breath offensive; liver enlarged. B. P. 112. First cardiac sound prolonged at apex.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Aug. 19	0·14	0	0	2	22	1847	0
23	0·18	0	tr	23	48	2049	0
27	0·17	tr	38	9	52	2725	0
30	0·17	(tr)	0	2	9	1400	0

Notes. Mild case. Recent. Carbohydrate tolerance good. No ketonuria. Blood-sugar low; not reduced by treatment; varied with carbohydrate rather than with glycosuria.

Renal threshold low, steady.

No. 816. ♂ Aged 45. Admitted August, 1918.

1913, overworked; glycosuria discovered; no symptoms; glycosuria always easily reduced by diet.

Complaint on admission. No symptoms.

Examination. Stout subject. B. P. 115.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Aug. 6	0·22	tr	tr	23	90	2235	0
9	0·21	tr	tr	23	117	2125	0
12	0·18	0	0	1	1	48	0
16	0·16	0	0	2	34	1485	0
19	0·17	0	0	12	55	1815	(tr) Ac
22	0·14	0	0	22	72	1435	0
27	0·16	tr	0	12	111	2189	0
Sept. 2	0·16	0	0	2	1	48	0
6	0·16	0	0	2	1	48	0
9	0·17	tr	—	2	67	1633	0

Notes. Slight case. Long standing. Carbohydrate tolerance good. Ketonuria very slight.

Blood-sugar low; reduced by treatment; varied with glycosuria rather than with carbohydrate.

Renal threshold low, steady.

No. 834. ♂ Aged 53. Admitted September, 1918.

1908, acute onset; became sugar-free on strict diet; gave up diet later. 1912, occasional weakness. 1913, had 'gangrene' above right ankle; cleared up. 1913–14, became drowsy and suffered from cold feet.

Complaint on admission. Thirst. Polyuria; frequency of micturition. Weakness and stiffness of legs; cold feet. Drowsiness. Tachycardia and intermittent pulse.

Examination. Fat. Bad teeth; pyorrhoea.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Sept. 6	0·20	47	40	2	75	2215	0
10	0·14	17	7	2	34	2254	0
13	0·14	4	tr	2	13	2082	0
17	0·16	0	0	1	2	506	tr Ac
20	0·17	0	0	2	20	2879	tr ,,
24	0·14	0	0	13	33	2752	tr ,,
27	0·19	0	(tr)	21	48	2247	tr ,,
Oct. 1	0·18	0	(tr)	22	70	2692	(tr) ,,

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar low; persistent; followed glycosuria rather than carbohydrate.

Renal threshold low, rising.

No. 843. ♂ Aged 48. Admitted August, 1918.

1901, colitis; constant tiredness. 1910, glycosuria discovered, but could always get sugar-free by diet. 1916, weaker; suffered from nervous sensations in head; sleeping badly. 1918, April, weaker than ever.

Complaint on admission. Weakness. Depression. Pains in legs. Sensations of pressure and pricking in head. Constipation.

Examination. Florid; robust; nervous. Tongue flabby; breath sweet; pyorrhoea. B. P. 130; artery thickened. Slight emphysema.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Sept. 2	0·15	31	11	2	13	2406	tr Ac
6	0·24	6	0	1	1	48	0
10	0·17	tr	(tr)	1	2	486	1 Ac
13	0·16	0	0	1	5	1256	tr ,,
17	0·12	0	0	2	9	1782	tr ,,
20	0·15	0	6	2	17	1951	tr ,,
24	0·15	(tr)	3	2	14	2177	tr ,,
Oct. 1	0·20	37	21	2	38	2700	tr ,,
4	0·21	47	39	14	38	3165	tr ,,

Notes. Mild case. Long standing. Carbohydrate tolerance bad. Ketonuria slight.

Blood-sugar high; not reduced by treatment; varied most closely with glycosuria.

Renal threshold low, steady.

No. 850. ♀ Aged 51. Admitted September, 1918.

Seven months before admission lost weight and was easily tired. July, 1918, thirst and polyuria.

Complaint on admission. Polyuria. Bad thirst. Constipation; neuritis.

Examination. Thin; sallow. Tongue furred; breath sweet. Pulse 84. B. P. 138.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Sept. 12	0·17	+	44	2	13	2198	1 Ac
17	0·18	11	22	2	13	2274	2 ,,
20	0·15	0	0	1	1	36	1 ,,
24	0·14	0	0	2	3	686	1 ,,
27	0·15	0	0	2	11	1324	tr ,,
Oct. 1	0·18	10	(tr)	22	22	1997	tr ,,
4	0·18	tr	tr	2	37	2153	(tr) ,,
8	0·15	0	0	2	41	2078	0
15	0·20	0	14	24	70	2198	(tr) ,,
18	0·22	0	0	2	11	1501	0

Notes. Mild case. Recent. Carbohydrate tolerance good. Ketonuria considerable; reduced by treatment.

Blood-sugar low; not reduced by treatment; varied with carbohydrate rather than with glycosuria.

Renal threshold low, rising.

No. 864. ♀ Aged 57. Admitted September, 1918.

Suffered from frequent colds. August, 1918, loss of flesh, cramp; glycosuria discovered; felt miserable and depressed.

Complaint on admission. Loss of weight.

Examination. Drowsy, tired, flushed. Breath sweet; tongue furred, fissured; teeth bad; pyorrhoea. Pulse 100; artery thickened. B. P. 135; short cardiac systolic bruit. Knee-jerks very sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Sept. 17	0·19	65	52	2	17	2223	2 Ac
20	0·17	47	45	2	10	1577	2 ,,
24	0·17	0	0	1	1	48	tr ,,
27	0·17	0	0	1	2	313	1 ,,
Oct. 1	0·17	0	(tr)	2	7	1222	tr ,,
4	0·16	(tr)	(tr)	2	15	1585	(tr) ,,
8	0·18	14	tr	2	26	1464	0
11	0·18	0	0	2	4	623	(tr) ,,
15	0·20	(tr)	tr	17	31	1871	(tr) ,,
18	0·15	0	0	1	1	48	(tr) ,,
22	0·23	11	tr	2	15	1408	(tr) ,,
25	0·23	(tr)	tr	2	4	635	(tr) ,,
29	0·17	10	0	1	2	461	(tr) ,,
Nov. 1	0·16	tr	9	2	14	1407	(tr) ,,
5	0·17	21	16	2	9	1470	(tr) ,,
8	0·19	0	tr	2	8	1047	(tr) ,,
12	0·17	12	16	2	17	2020	—

Notes. Mild case. Recent. Carbohydrate tolerance bad. Ketonuria considerable; reduced by treatment.

Blood-sugar low; not reduced by treatment; varied with glycosuria rather than with carbohydrate.

Renal threshold low, steady.

No. 868. ♀ Aged 55. Admitted October, 1918.

1911, arthritis. March, 1918, thirst; glycosuria discovered.

Complaint on admission. Bad thirst. Polyuria. Arthritis. Sleeping badly. Tiredness.

Examination. Pale, thin, dry skin. Tongue furred; breath sweet. Knee-jerks sluggish. B. P. 120.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Oct. 8	0·19	57	55	2	9	1161	5 Ac
11	0·18	(tr)	0	1	1	48	4 Ox
15	0·15	0	0	1	3	659	6 ,,
18	0·16	0	tr	2	7	1247	1 ,,
22	0·19	0	0	1	4	1044	2 ,,
25	0·19	0	0	2	19	1414	tr ,,
29	0·20	0	8	21	21	1888	tr ,,
Nov. 1	0·18	tr	10	2	14	1490	tr ,,
5	0·13	0	0	2	20	1712	tr ,,
8	0·16	0	0	12	36	1791	tr ,,

Notes. Mild case. Recent. Carbohydrate tolerance good. Ketonuria considerable; improved under treatment.

Blood-sugar low; reduced by treatment; followed carbohydrate rather than glycosuria.

Renal threshold low, rising.

No. 874. ♂ Aged 60. Admitted November, 1918.

1903, glycosuria discovered at insurance examination. 1914, was again refused insurance. Six to twelve months before admission noticed dryness of mouth, thirst, and polyuria.

Complaint on admission. Feeling fit for nothing. Loss of weight. Drowsiness. Lack of concentration and memory. Poor appetite.

Examination. Breath sweet; tongue pale; liver enlarged. Radial artery thickened; B. P. 115; heart sounds softened. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Nov. 6	0·26	+	63		—	ord. diet	(tr) Ac
8	0·27	22	99	42	—	ord. diet	tr ,,
12	0·20	27	22	19	60	220	tr ,,
15	0·17	8	tr	2	14	2391	tr ,,
19	0·16	0	0	2	8	1312	tr ,,
22	0·12	0	0	2	22	2129	tr ,,
26	0·14	0	0	2	14	2248	tr ,,
29	0·15	0	tr	2	52	2297	tr ,,

Complications. Slight albuminuria.

Notes. Mild case. Long standing. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar high; reduced by treatment; followed glycosuria more closely than carbohydrate.

Renal threshold low, falling a little.

No. 885. ♂ Aged 47. Admitted November, 1918.

Overworking. November, 1917, glycosuria discovered; became sugar-free on moderately restricted diet; began to lose weight. June, 1918, glycosuria returned. October, 1918, bad influenza; sugar-free afterwards.

Complaint on admission. Lack of energy. Long-standing constipation.

Examination. Tongue slightly furred; some pyorrhoea. Pulse 92; artery thickened; B. P. 152. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Nov. 23	0·17	+ +	0	2	109	2659	0
26	0·16	0	0	2	25	2307	0
29	0·12	0	0	1	1	48	1 Ac
Dec. 3	0·13	0	0	2	51	2151	1 ,,
6	0·18	0	0	19	56	2844	tr ,,
10	0·14	0	0	2	46	2573	0
13	0·14	0	0	13	63	2596	0
17	0·12	0	0	2	26	2580	0

Notes. Slight case. Recent. Carbohydrate tolerance good. Ketonuria slight.

Blood-sugar low; reduced by treatment; followed carbohydrate more closely than glycosuria.

Renal threshold low, steady.

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No. 899. ♂ Aged 54. Admitted December, 1918.

1913, had noticed unusual thirst for five years; glycosuria discovered. Improved on diet. For one year had been losing little weight. For six weeks had nausea and abdominal pain, and lost much weight.

Complaint on admission. Tiredness. Weakness. Dryness of mouth. Dimness of vision.

Examination. Thin. Tongue furred; some pyorrhoea; breath offensive and smelling of acetone. Pulse 90; B. P. 125. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Dec. 10	0·26	+	120	2	—	—	+ Ac
13	0·19	96	86	2	10	1440	5 „
17	0·21	60	75	2	10	1490	5 „
20	0·18	71	63	2	2	345	3 „
24	0·16	27	55	2	9	1574	4 „
27	0·18	44	32	2	9	1535	3 „
31	0·21	0	(tr)	1	1	168	1 „
Jan. 3	0·20	15	36	1	6	1184	1 „
7	0·17	(tr)	10	1	2	463	tr „
10	0·19	18	25	2	9	1617	1 „
14	0·16	0	0	2	2	458	1 „
17	0·22	27	39	8	9	1421	2 „
21	0·21	52	—	2	20	1590	—

Complications. Occasional faint traces of albumin in urine.

Notes. Severe case. Recent. Carbohydrate tolerance bad. Ketonuria considerable; improved under treatment.

Blood-sugar high; not much reduced by treatment; varied more closely with glycosuria than with carbohydrate.

Renal threshold low, fluctuating.

No. 907. ♂ Aged 46. Admitted December, 1918.

1916, loss of weight. February, 1916, glycosuria; but easily made sugar-free by diet. 1917, felt well; but had no urine tests. January, 1918, glycosuria returned. July, 1918, trace remained.

Complaint on admission. Slight loss of weight.

Examination. B. P. 120.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Dec. 6	0·18	29	22	2	39	2364	0
10	0·15	24	13	2	11	1745	(tr) Ac
13	0·11	0	0	1	1	36	(tr) „
17	0·14	(tr)	tr	1	4	625	1 „
20	0·12	0	0	1	4	645	tr „
27	0·17	0	0	2	9	1535	tr „
31	0·18	tr	2	1	7	793	tr „
Jan. 3	0·18	tr	0	1	9	162	tr „

Notes. Mild case. Long standing. Carbohydrate tolerance bad. Ketonuria slight.

Blood-sugar low; not reduced by treatment; varied equally with glycosuria and carbohydrate.

Renal threshold low, rising.

No. 919. ♀ Aged 51. Admitted January, 1919.

1899, injury to head; noticed thirst and loss of weight; soon after glycosuria discovered. Patient kept well on diet. 1918, June, noticed loss of strength and weight.

Complaint on admission. Frequent abdominal pain and diarrhoea. Increasing weakness for six months accompanied by loss of weight and palpitation. Praecordial discomfort.

Examination. Thin; nervous. Bad teeth; pyorrhoea. Artery thickened; heart irregular; B. P. 120.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Jan. 14	0·11	10	5	2	13	2454	0
17	0·12	14	11	2	14	2335	(tr) Ac
21	0·15	9	10	2	14	2287	(tr) ,,
24	0·13	12	18	2	26	2479	0
28	0·13	6	tr	2	35	2494	0
31	0·14	10	7	2	41	2571	0
Feb. 4	0·12	19	9	2	35	2898	0
7	0·13	tr	tr	2	15	2291	(tr) ,,
14	0·13	7	7	2	34	2298	(tr) ,,
21	0·15	tr	0	2	46	2453	(tr) ,,
28	0·15	0	tr	2	44	2508	tr ,,

Complications. Occasional faint traces of albumin in urine.

Notes. Mild case. Long standing. Carbohydrate tolerance bad. Ketonuria slight.

Blood-sugar low; not reduced by treatment; varied with carbohydrate rather than with glycosuria.

Renal threshold low, rising.

No. 920. ♂ Aged 44. Admitted February, 1919.

1915, acute onset.

Complaint on admission. Thirst. Polyuria. Weakness; loss of weight. Drowsiness. Oedema of legs. Indigestion.

Examination. Flushed; skin yellow. Teeth deficient and bad; pyorrhoea; tongue raw. Knee-jerks sluggish.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria Grm. in 24 hours.
Feb. 8	0·22	126	118	21	—	—	1 Ac
11	0·23	53	107	13	66	2737	4 ,,
14	0·22	92	116	2	15	2470	3 ,,
18	0·19	102	81	2	13	2425	4 ,,
21	0·23	81	59	2	19	2395	3 ,,
25	0·21	77	82	2	24	2458	3 ,,
28	0·21	45	77	2	24	2323	2 ,,

Complications. Occasional slight traces of albumin in urine.

Notes. Severe case. Long standing. Carbohydrate tolerance bad. Ketonuria considerable; persistent.

Blood-sugar high; not much reduced by treatment; varied roughly with carbohydrate, but not with glycosuria.

Renal threshold low.

No. 945. ♂ Aged 46. Admitted March, 1919.

November, 1918, loss of weight and polyuria noticed.

Complaint on admission. Polyuria. Cramps; weakness in knees. Flatulence. Blurred vision in left eye.

Examination. Thin. B.P. 118.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
Mar. 4	0·22	—	98	2	16	2938	1 Ac
7	0·20	21	31	1	1	48	1 „
11	0·15	0	0	1	1	48	1 „
14	0·21	tr	tr	1	2	463	1 „
18	0·17	0	0	1	2	343	tr „
21	0·17	0	5	1	3	861	tr „
25	0·18	tr	15	1	3	657	tr „
28	0·17	tr	11	1	6	608	tr „
Apr. 1	0·18	29	40	2	9	1406	1 „
4	0·20	34	31	2	10	1290	1 „
8	0·21	50	19	2	9	1412	tr „

Notes. Severe case. Recent. Carbohydrate tolerance bad. Ketonuria considerable; improved under treatment.

Blood-sugar high; not much reduced by treatment; varied with glycosuria rather than with carbohydrate.

Renal threshold low, steady.

No. 1157. ♀ Aged 69. Admitted June, 1919.

1914, suffered from cerebral or heart attack; much glycosuria discovered afterwards, but cleared up quickly. 1918, caught a chill, followed by bronchopneumonia; no glycosuria. Week before admission developed facial paralysis while motoring; glycosuria ensued.

Complaint on admission. No symptoms.

Examination. Tongue red; little pyorrhoea. Faint, short, apical systolic bruit. B.P. 140. Right facial paralysis; electrical reactions normal.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
June 24	0·32	—	47	22	—	—	0
27	0·29	29	31	13	68	2461	0
July 1	0·21	13	11	24	33	1874	0
4	0·25	tr	tr	2	16	1735	0
8	0·16	tr	tr	2	11	1574	0
15	0·20	0	0	2	13	1715	0
18	0·24	0	1	13	23	1508	0
22	0·21	0	0	12	22	1889	0
25	0·21	tr	8	22	47	2408	0

Notes. Mild case. Long standing. Carbohydrate tolerance bad. No ketonuria.

Blood-sugar high; not much reduced by treatment; varied with carbohydrate rather than with glycosuria.

Renal threshold high, fluctuating.

No. 1167. ♀ Aged 47. Admitted July, 1919.

1914, noticed thirst and glycosuria; did well on treatment.

Complaint on admission. Thirst. Weakness. Pains in head.

Examination. Stout. B.P. 130. Râles at left base.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 8	0·23	15	over 7	13	51	1874	0
11	0·31	—	—	2	14	2339	0
15	0·19	tr	0	2	15	2205	0
18	0·19	0	0	1	4	962	0
22	0·20	0	0	13	27	1799	0
25	0·22	0	0	13	41	1746	0
29	0·22	0	0	13	64	1500	0
Aug. 1	0·28	tr	0	18	83	1791	0
5	0·27	tr	tr	24	79	1500	0
8	0·27	0	tr	13	40	2291	0
12	0·25	0	0	2	32	2035	0
15	0·29	0	0	11	35	2026	0
19	0·22	tr	tr	22	55	2556	0
22	0·28	tr	tr	22	54	2543	0

Notes. Mild case. Long standing. Carbohydrate tolerance good. No ketonuria.

Blood-sugar high; not reduced by treatment; varied with carbohydrate rather than with glycosuria.

Renal threshold high, fluctuating.

No. 1214. ♂ Aged 22. Admitted July, 1919.

1916, serving in Mesopotamia; developed malaria, followed by measles. 1919, January, noticed thirst, loss of weight, polyuria; glycosuria discovered. Improved under treatment.

Complaint on admission. Polyuria. Still feeling weak. Occasional thirst.

Examination. Flushed. Tongue red; teeth bad; breath smelt of acetone; abdomen distended. Pulse 88.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 18	0·28	94	135	45	58	2841	2 Ac
22	0·22	61	82	2	58	2723	1 „
25	0·25	50	29	2	9	1511	3 „
29	0·23	tr	0	1	1	36	+ „
Aug. 1	0·23	0	0	1	2	373	+ „
5	0·22	0	0	2	9	1401	0
8	0·24	0	0	2	1	48	0
12	0·26	0	0	2	15	1421	0
15	0·22	0	0	2	18	1601	0
19	0·24	0	0	2	30	1402	0
21	0·23	0	0	2	46	1855	0
25	0·22	0	0	2	53	2265	0
28	0·23	0	0	13	1	48	0
Sept. 1	0·22	0	tr	13	71	1733	0
4	0·25	tr	0	32	1	48	0
8	0·16	tr	tr	32	84	2234	0
12	0·18	0	0	13	53	1875	0
15	0·13	0	0	24	81	2768	0
18	0·19	0	tr	25	92	3087	0
22	0·19	0	0	24	72	2827	0
26	0·20	0	0	24	94	2918	0
30	0·12	tr	tr	24	94	2614	0

Notes. Severe case. Recent. Carbohydrate tolerance good. Ketonuria considerable; improved under treatment.

Blood-sugar high; reduced by treatment; did not vary closely with either glycosuria or carbohydrate.

Renal threshold high, fluctuating.

No. 1224. ♀ Aged 48. Admitted July, 1919.

1913, cystitis. 1918, in summer, noticed weakness and thirst; glycosuria discovered in September; thirst became normal under treatment.

Complaint on admission. Loss of strength.

Examination. Hb. 58 per cent. B. P. 150.

Date.	Blood-sugar %.	Sugar in Urine. Grm. Previous 24 hours.	Day of Observation.	Carbohydrate in Preceding Meal.	Total Carbohydrate Preceding Day.	Total Calories Preceding Day.	'Ketonuria.' Grm. in 24 hours.
July 31	0·18	tr	3	1	6	1348	0
Aug. 6	0·18	—	0	2	9	1511	0
8	0·22	0	tr	2	9	1448	0
12	0·26	6	tr	2	10	1828	0
15	0·26	0	0	2	9	1456	0
18	0·29	tr	0	2	25	1486	0
22	0·31	7	tr	2	9	1455	0
26	0·20	0	0	11	16	1788	0
Sept. 2	0·21	—	—	2	9	1378	0
5	0·22	0	0	2	20	1494	0
12	0·25	0	0	2	10	1482	0
19	0·21	0	tr	2	7	1525	0
23	0·20	10	6	11	33	1701	0
26	0·20	0	0	2	11	1652	0
30	0·18	14	10	2	45	2165	0

Notes. Mild case. Recent. Carbohydrate tolerance bad. No ketonuria.

Blood-sugar high; not reduced by treatment; follows glycosuria rather than carbohydrate.

Renal threshold high, fluctuating.

THE DIAGNOSIS OF DISEASES OF THE PANCREAS, WITH SPECIAL REFERENCE TO DIASTASE IN THE URINE

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I. *Introduction.*

The importance of the pancreas for the maintenance of life has been known for a long time, but it is only in recent years that its place in medicine and surgery has been clearly recognized. The methods of diagnosis of diseases of this gland have so far not been worked out, and this phase of the problem may still be regarded as in its infancy. In view of the manifold functions of the pancreas, and their vital necessity for the economy of the body, it behoves us to use every means available to determine the possible nature and extent of the commoner diseases to which it is prone. It is clear from this very multiplicity of function that not one but several tests must be applied in any given case before a conclusion can be reached as to whether the pancreas is diseased or not. The object of this paper is to describe the various tests for functional activity of the pancreas, and to attempt to appraise their individual or collective worth in diagnosis. The observations have extended over a period of years, and practically all the known tests have received an extended trial. No new tests have been devised, but simply modifications in technique, which have suggested themselves as the work progressed, have been introduced into the various methods.

The Schorstein Lecture delivered by Sir Archibald Garrod (1) gives a complete and excellent survey of the work done, and the writer would here express his indebtedness to his teacher, Sir Archibald Garrod, for much valuable help and encouragement. This work owes its inception to his stimulating influence, and this influence is exemplified in every page of the present paper. The same conclusions have been arrived at, and needless to say the results have been discussed, and additional weight added thereto by such support and advice so freely given.

II. *The Physiology and Biochemistry of the Pancreas.*

There is no organ of the body where such a marked disparity exists between its well-established physiological importance and our powers of estimating its

functional capacity in clinical medicine. The pancreas possesses two functions of the greatest importance to the maintenance of metabolism, firstly as a digestive organ, and secondly as an organ providing an internal secretion, which controls carbohydrate metabolism.

The true functions of the gland were only established in the last century, and we owe this to a group of great experimental physiologists, particularly Claude Bernard and his school. They established the fact that the secretion from the pancreas contains ferments for the digestion of all three classes of food-stuffs, the proteins, the carbohydrates, and fats. In the latter half of the century the association of the pancreas with diabetes mellitus was clearly expounded by von Mering and Minkowski (1*). The discovery that total extirpation of the pancreas leads to diabetes mellitus was an epoch-making discovery, and led to the conception of an internal secretion, which in some way controlled carbohydrate metabolism.

Since this discovery of these two main functions an immense amount of detailed work has pervaded the literature, but delve into the subject where you will, abundant evidence of the vast difficulties that beset the study of the pancreas will be forthcoming.

Pathologists, however, have fallen far behind in this march of progress and comparative rapid acquisition of knowledge, but they have not been so favourably placed, chiefly on account of the difficulties of experimental work and the inconclusive morbid anatomical findings. Numerous tests have been devised, based upon the known functions of the gland, but the tendency of each individual worker has been to confine himself to one or two functional tests to the exclusion of all others. That this has met with failure is well known, and is further emphasized by reference to the cases described in this paper. It would appear that hitherto no one has attempted to apply all the various functional tests in any one case of suspected disease of the pancreas, and then to sum up the evidence obtained and clearly state their individual or collective value. This is the object of the present communication. The second object, and, strictly speaking, the primary one, was to ascertain, if possible, whether any light could be thrown on the causation of diabetes mellitus. The recent work of Allen in America affords very strong evidence for implicating the pancreas. In my work it is to be regretted that so far no evidence of disturbance of function has been detected, but the results have given an insight into the possible site of disease so that the negative evidence becomes of real value. The conception of a definite balance of function between the various ductless glands leads one to speculate that the pancreas may be at fault, because it fails to balance its secretion against one of the other glands. The results with the Loewi adrenalin mydriasis test are of particular interest in this connexion, and will be referred to later in this paper.

III. *Clinical Features.*

The clinical diagnosis of diseases of the pancreas is of the greatest importance, and necessarily occupies the first place in any discussion of its commoner affections. From the point of view of the clinician this is a matter of some difficulty. We might almost introduce a medical aphorism in the clinical diagnosis of diseases of the pancreas—'it is easy to forget the pancreas, but still more difficult to remember it.' The physician who remembers the pancreas when confronted with certain well-defined clinical features, and places it under suspicion, has the satisfaction of seeing his diagnosis confirmed, and frequently with great benefit to his patient. By inspection, palpation, blood examination, and a careful study of the symptoms, particularly lumbar pain, tenderness, the presence of a tumour, and presence of pressure effects on neighbouring viscera, he obtains valuable data, and these have to be assessed at their true value. Features, such as jaundice, wasting, and anaemia may obscure the diagnosis, more particularly when we realize that it is rarely that the pancreas is alone involved. Of the symptoms, epigastric pain and tenderness would appear to be the most common, usually deep-seated, and radiating upwards to the right shoulder. The wasting and anaemia which are frequent concomitants can be explained by the deficiency of pancreatic ferments, and consequently lack of assimilation of digested foodstuffs from the alimentary canal. This deficiency also accounts for the large and bulky stools, and their characteristic appearance, which is likened to finely-divided asbestos, but often described as clay-coloured. The urinary changes are not very characteristic, but the presence of glycosuria may shed a ray of light on an otherwise obscure case, and the presence of bile pigments in quantity will point to involvement of the common bile duct. The occurrence of oxaluria has been suggested as characteristic of pancreatic diseases, but although frequently present it cannot be said that it is in any way an indication of pancreatic insufficiency. It is much more likely to be due to the associated intestinal changes secondary to abnormal digestion in the alimentary canal. The same applies to indicanuria.

In assessing the value of the clinical data it must be clearly recognized that some functions of the pancreas may be subserved by other organs when the former is diseased, and again one or more functions may be disturbed, leaving the others quite unaffected. Bearing these points in mind the clinician is able to gain much valuable and useful information, which can be applied to the diagnosis and treatment of his patient, with mutual gain to all concerned. Finally, we have the opportunity of advising exploratory laparotomy as a valuable aid, and often an indispensable adjunct in the present state of our knowledge.

IV. *The Methods used for testing the Functional Activity of the Pancreas.*

The tests so far devised depend entirely on the two chief functions of the pancreas—the digestion of food-stuffs in the intestine, and the internal secretion controlling carbohydrate metabolism. In discussing the tests, therefore, it is convenient to consider them under these two headings, and since the digestive functions are more easily determined, it follows that the tests under this heading are more numerous, and consequently have received considerably more attention. A full description of these tests has been given by Sladden (14, 15) in two valuable papers, and the reader is referred to these for information upon the subject.

1. Tests for the digestive ferments secreted into the alimentary canal, and depending upon a diminution or complete absence of these ferments. Most of these tests have necessarily to be carried out on the stomach contents, or the faeces.

(*a*) *Azotorrhoea.* With the associated creatorrhoea, combining the Schmidt test, the Kashiwado modification of the former (3), the Sahli test, and the tryptic activity of the faeces by the serum agar plate method, and the casein method of Gross.

(*b*) *Steatorrhoea.* Including analysis of the fat content of the faeces, the 'sajodin' test of Winternitz (7), and tests for lipolytic activity of the faeces.

(*c*) *Diastase.* The presence of microscopical starch in the faeces, and the diastatic index of the faeces.

(*d*) The oil-test breakfast, combining the estimation of all three digestive ferments.

2. Tests depending upon other functions of the pancreas:

(*a*) The general characters of the urine.

(*b*) The diastase content of the urine (8, 9).

(*c*) The Cammidge pancreatic reaction (10).

(*d*) The Loewi adrenalin mydriasis reaction (11).

(*e*) The glucose tolerance test.

The pancreas being the only gland in the body which furnishes an enzyme for each class of food-stuff, it would appear possible to apply digestion tests to ascertain whether there is any marked deficiency in one or all of these three ferments. In practice, however, it is much more difficult than at first appears, especially when we attempt to estimate clinically its functional capacity. The ferments undergo considerable modifications in their passage through the alimentary canal, and we meet with additional difficulties due to the presence of erepsin, a protein-digesting ferment in the small intestines, and last but by no means least considerable bacterial fermentation. Further, we cannot control the duration of passage of the gastro-intestinal contents, and if this is either increased or delayed the composition of the faeces is thereby considerably altered. All that we can do is to adopt precautions, and consider all possible fallacies, so as to avoid sources of grave error in the results.

To control the composition of the faeces a standard diet has been adopted, based largely upon that devised by Schmidt. This diet yields residues which are sufficiently characteristic, and there is the additional advantage that we have abundant normal controls with which a comparison can be made. The diet consists of 2 eggs, 1½ litres of milk, 100 grm. of toast, 50 grm. of butter, 125 grm. of raw beef, 190 grm. of potatoes, and 80 grm. of oatmeal. This diet contains about 102 grm. of protein, 111 grm. of fat, 191 grm. of carbohydrate, and yields about 2,234 calories of energy. In hospital practice the constituents of the diet are spread out over the day in the following routine order:

Early morning: ½ litre (17½ oz.) of milk, 50 grm. (1¾ oz.) of toast. Breakfast, 9 a.m.: ½ litre (17½ oz.) of oatmeal gruel made from 40 grm. (1½ oz.) of oatmeal, 200 grm. (7 oz.) of milk, 10 grm. (⅓ oz.) of butter, 300 grm. (10½ oz.) of water, and 1 egg added.

Lunch: 125 grm. (4½ oz.) of raw beef, minced and fried in 20 grm. (¾ oz.) of butter, 250 grm. (9 oz.) of mashed potato made from 190 grm. (7 oz.) of mashed potato, 100 grm. (3½ oz.) of milk, and 10 grm. (⅓ oz.) of butter.

Tea: exactly the same as the early morning meal.

Supper: the same as taken at breakfast.

This diet is very simple and can be easily adopted in the hospital wards, and it is only rarely that we find the patient is unable to take it. If milk does not agree cocoa is substituted, and this is made up as follows: 20 grm. (⅔ oz.) of cocoa powder, 10 grm. (⅓ oz.) of sugar, 400 grm. (14 oz.) of water, and 100 grm. (3 oz.) of milk. Previous to the adoption of this diet the patient is given a purgative, and usually after two days of the diet a representative specimen of the faeces can be obtained, but no fixed rule can, of course, be laid down as particular cases are found to vary in this respect.

The bulkiness of the stools is an important feature, and one which can be readily judged by this special diet. Normally, the average weight of the dried faeces is about 55 grm., with a maximum of 62 grm. and a minimum of 45 grm. A marked rise in the total dried weight is therefore of importance.

The tests applied to the faeces obtained on such a diet necessarily resolve themselves into determining ferment activities. Unfortunately, we have no means of collecting pure pancreatic juice as it flows down the pancreatic duct, but it should be borne in mind that about one pint or even more of this pancreatic juice pours through the ampulla of Vater into the duodenum every day. This secretion, which is alkaline, and contains quantities of alkaline salts, will necessarily modify the composition of the faeces quite apart from any digestive changes which may have taken place. This is the reason why an estimation of the inorganic ash in the faeces is always carried out, since very low values are almost constantly present when there is complete obstruction to the pancreatic duct and also the common bile duct.

(*a*) *Azotorrhoea and Creatorrhoea.* The pancreas supplies the precursor of the ferment trypsin, which is capable of digesting proteins and peptones with the production of amino acids in a form suitable for absorption into the blood-

stream. In the absence of pancreatic juice from the intestine such proteins, or their partially digested products, escape digestion to a large extent, and pass out in the faeces in an unchanged condition.

The chief nitrogenous fraction of an ordinary diet is meat, and it follows that in the absence of trypsin this will escape complete digestion, and evidence will not be wanting of its presence in the faeces in a recognizable form. A simple microscopical preparation is all that is required to demonstrate the presence of undigested muscle fibres. They may be recognized by their abundance, the yellow colour, the characteristic striations, and possibly the presence of nuclei. This phenomenon is known as creatorrhoea, and is a most valuable sign of pancreatic insufficiency. If a film preparation is made from the faeces of a normal healthy individual on the special diet, only one or two muscle fibres will be seen in each field, or perhaps none at all, and those actually found will be devoid of shape and striations.

The tests of tryptic activity may be regarded as a useful aid, but are certainly not absolute in their indications, and serve to establish the main view adopted in this paper that no one test can be positively relied upon. A positive result showing the absence of trypsin from the alimentary tract is, of course, much more valuable than a negative result, as with every other test so far devised.

(*b*) *Steatorrhoea.* The association of the so-called 'fatty stools' with disease of the pancreas has been recognized for a long time, and it is often this phenomenon which calls the attention of the physician to the nature of the case. Frequently it can be recognized by the naked eye; often by simple microscopical examination, especially if iodine is used as a stain; but in cases where the fat is finely divided only by careful chemical analysis. The presence or absence of bile from the intestine, however, produces profound modifications of the fat content, and so must always be taken into account.

Unfortunately we rarely find such 'clean-cut' results in cases of pancreatic insufficiency, and this is partly due to deficiencies in our methods of analysis. The presence of urobilin is always looked for and the most delicate tests applied. Extraction with amyl alcohol of a portion of the stools and treatment of the extract with a fresh alcoholic solution of zinc acetate are always used. The absence of a trace of colour, fluorescence, and the characteristic absorption band of urobilin when examined spectroscopically, conclusively proves that no bile is entering the intestine.

The analysis of the various forms of fat in the stools is carried out on representative samples of the dried faeces, using the Soxhlet method of extraction. The analysis of the faeces involves the adoption of a complex technique, but in order to draw any definite conclusions data as regards the following fractions must be obtained:

(1) The total percentage of fat in the dried faeces.
(2) The percentage of unsplit or neutral fat.
(3) The percentage of free fatty acids.
(4) The percentage of soaps.

The figures for 3 and 4, therefore, give the total amount of split fat in the faeces. The ratio of these two figures to the total fat gives an indication of the efficiency of the pancreatic secretion as regards its lipolytic activity. This method has been followed throughout the present research, and the results obtained have fully justified the time and labour involved.

The sajodin test of Winternitz (7) has also received an extended trial, but the results have been very disappointing. The object of this test is to administer iodine containing fats, and to detect the liberated iodine in the urine about five hours after ingestion. The best iodine containing fat for this purpose is that known as 'sajodin', which is chemically the calcium salt of iodo-behenic acid. The procedure I have adopted is to give one tablet of 'sajodin' containing $7\frac{1}{2}$ grains of the salt either with or immediately following a good meal. In two normal healthy individuals, including the writer, iodine appeared in the urine three to five hours afterwards, the total amount being entirely eliminated within one hour of its first appearance. In several cases of undoubted pancreatic disease, no iodine was found in the urine even forty-eight hours after administration. The sajodin, however, requires the presence of bile salts before it can be acted upon by the pancreatic juice, consequently we find the test is positive in all cases of jaundice where there is complete or partial obstruction to the common bile duct. The test has been tried in a variety of cases, and given positive results in cirrhosis of the liver, hydatid cyst of the liver, and other diseases. The experiments carried out *in vitro* showed that sajodin was rendered soluble by the action of pancreatic juice or pancreatic extracts. This led me into error, as I found that it was practically impossible to obtain an active pancreatic extract without contamination with bile salts. Apart from the steapsin of the pancreas, digestion with very strong acids is the only method by which the iodine can be liberated. At first I was inclined to regard this as a most valuable test, but it has failed me in so many important cases that I have now discarded it as of no value.

Diastase. The presence of starch granules in a microscopical preparation has been regarded as of diagnostic value in pancreatic insufficiency, but after an examination of many hundreds of faeces of all types, I can state without hesitation that it is an extremely rare phenomenon. The estimation of the diastase in the faeces on the same lines as that used for the urine has also been tried. In my experience it is valueless, since a normal index is so frequently found in cases of undoubted pancreatic insufficiency. Starch digestion in the alimentary canal of Europeans is remarkably complete, and I infer that there are ferments, other than diastase (amylase), in the pancreatic juice which are capable of exerting this function. During my service in India I had occasion to determine the diastase content of the faeces and found it to be normal, although microscopical examination showed abundance of starch granules in every case. The diet of such individuals is so rich in starch, that the alimentary canal is incapable of dealing with it either normally or abnormally.

The occurrence of starch in the stools is due either to undue peristalsis in

the intestine, or to an excessive intake of starchy foods, and in my opinion has no reference to any deficiency of pancreatic juice.

(*d*) *The oil-test breakfast.* This test may be dismissed in a few words. Apart from its unpleasantness to the patient the results of a trial of four cases were so indefinite that it was discarded. Trypsin is really the only ferment that can be determined with any degree of accuracy, and the activity of this ferment is influenced by so many extraneous factors, particularly the acidity of the gastric contents, as to render the results of doubtful value. In a case of carcinoma of the pylorus a diminished tryptic content of the stomach contents was found after the oil breakfast, although there was abundant evidence of regurgitation. The pancreas was found to be unaffected, and this test was the only positive indication for pancreatic insufficiency.

2. Tests depending upon other functions of the pancreas.

(*a*) *The general characters of the urine.* This subject has already been considered under the heading of clinical features of diseases of the pancreas. The records given in the summary of cases will indicate the chief constituents most frequently sought for. Attention was paid more particularly to the occurrence of pigments, such as urobilin and bile pigments, also indican, and the presence or absence of abundant crystals of calcium oxalate in the urinary deposit. Finally, the absence of ethereal sulphates in pancreatic insufficiency has received attention.

(*b*) *The diastase content of the urine.* The presence of a ferment capable of digesting starch solutions when added to urine has been known for a very long time. The subject received new interest when, in 1908, Wohlgemuth (8) published his method of estimating the amount of diastase in the urine. He showed that in pancreatic disease the diastase content of the urine was markedly increased. Since these observations were recorded a number of workers have all obtained confirmatory evidence, but the best and most complete work is undoubtedly that of Corbett (9) in this country. He showed that there is normally a certain amount of diastase in the blood and that the same quantity is excreted by the kidneys.

If there is an increase of diastase in the blood then there is a corresponding increase in the amount of diastase in the urine provided that the kidneys are functionally unimpaired. The slightest damage to the renal epithelium leads either to a great diminution of diastase in the urine or to an increase depending upon the permeability of the kidney. Geyelin (12) came to similar conclusions as regards the influence of the kidneys in the removal of diastase from the blood. With regard to pancreatic diseases it is of interest to note that Wohlgemuth and Noguchi (13) found an increase of diastase in both blood and urine where the pancreas had been injured. The results of Corbett are also striking, and there seems to be no doubt that a high diastase value of the urine is in favour of pancreatic disease, whereas a normal or low value points to a normal pancreas. Some writers, however, have suggested that these high values are only obtained in the acute stages of the disease. These observations represented

the general trend of opinion when I first commenced my work upon the subject. The analysis of my results will be given later and compared with the other tests that have been applied. In carrying out the estimations I have followed the technique devised by Wohlgemuth in certain particulars, and the method of procedure adopted is as follows:

A full twenty-four hours' hourly collection of the urine is made into clean stoppered glass bottles, and the estimation is carried out as rapidly as possible after the full amount has been collected. The urine should be as free as possible from contamination, and where a twenty-four hourly specimen is unobtainable I generally advise a six-hourly collection, or better still a twelve-hourly collection. Apart from the fact that there may be a slight rise in the diastase content of the urine preceding a meal, followed by a fall immediately afterwards lasting for from three to four hours, the rise is so slight that it is almost negligible. Except for practical purposes it does not matter whether a fresh specimen or a twenty-four hours' hourly sample of urine is used. To preserve the urine when facilities for carrying out the test are not immediately available toluol is added. This will not affect the diastase, and, in fact, specimens may be kept for months or even years without showing any alteration in their diastase content. All other forms of preservative must be avoided, since I have found that in most cases they lead to immediate destruction of the ferment.

For the actual test only 2–3 c.c. of urine are required. The apparatus and chemical reagents required are:

(1) Ten clean dry test-tubes made of good glass, of equal bore, and of uniform thickness.

(2) Standard 10 c.c. burettes, graduated pipettes of 1 c.c. and 2 c.c. capacity.

(3) Pure distilled water.

(4) A carefully prepared solution of starch, made by dissolving 2 grm. of pure 'soluble' starch in 100 c.c. of pure 10 per cent. sodium chloride solution. This acts as a stock solution, and the standard starch solution is made up fresh as required. 5 c.c. of this stock solution are placed in a 100 c.c. measuring flask, and diluted up to the mark with pure distilled water. This solution now contains 0·1 grm. per cent. of soluble starch in a 0·5 per cent. solution of sodium chloride, and is the solution used in all the diastase estimations recorded in this paper.

(5) A 1/50 normal solution of iodine. This has to be made up fresh as required, since it does not keep well, particularly in the summer months. The iodine solution is stored in the dark in the 1/10 normal strength, and from this a fresh 1/50 normal solution is made by diluting 2 c.c. of the iodine solution up to 10 c.c. with distilled water. A specially prepared dropping pipette is always used with this solution to ensure that the same number of drops of dilute iodine are added to each tube when carrying out the estimation.

(6) A reliable water bath which is maintained at a temperature of 39° C. by means of a thermo-regulator.

(7) A wire cage to hold the test-tubes in place when immersed in the bath.

The tests are carried out as follows: The ten test-tubes are placed in a stand and numbered in sequence. 1 c.c. of the urine to be tested is added to tube No. 1 by means of a graduated pipette, and decreasing quantities in the remaining nine tubes. We have now a series of ten test-tubes containing various decreasing quantities of urine, and these are now made up to an equal volume—1 c.c. with distilled water. It has been found that by careful manipulation, and using a standard pipette, this method of dilution gives rise to only a slight error, at least insufficient to affect the estimation.

We thus have the following series of dilutions:

(1)	1	c.c. of urine.
(2)	0·5	„ „
(3)	0·4	„ „
(4)	0·1	„ „
(5)	0·08	„ „
(6)	0·06	„ „
(7)	0·04	„ „
(8)	0·02	„ „
(9)	0·01	„ „
(10)	0·008	„ „

All these ten tubes are now inserted into the wire cage and placed in the water bath for 15–30 minutes. This serves to bring the temperature of the mixtures up to the required level, and further activates the ferment present in the urine. The diluted starch solution is now run into each tube, 2 c.c. being used, and, after mixing, the tube is replaced in the wire cage. The wire cage is placed in the water bath and allowed to remain there for half an hour, after which time the cage is withdrawn, and placed under running water to cool the tubes to arrest any further ferment action. The ten tubes are replaced in the test-tube stand in their original order. By means of the fine-dropping pipette two drops of the freshly prepared iodine solution are added to each tube and the mixture shaken.

If the urine is normal, tubes 1, 2, and 3 will show a golden-yellow colour, indicating that the 2 c.c. of starch solution added has been completely digested by the diastase present in the urine, whilst tube 4 will have a reddish colour with no tinge of blue, tube 5 a violet tinge, and all the remaining tubes will be deep blue. In such a series tube 4 will give the reading required, since it is the tube where the starch has been digested as far as the dextrin stage. This red-coloured tube is taken as the limit tube when the above dilutions are used. After considerable experience with this method I prefer to adopt this reading rather than the somewhat indefinite mauve limit in Corbett's modification.

The calculation of the amount of diastase in the urine is now a simple matter, the result being expressed in terms of units of diastase. Thus tube 4 gives a red coloration and shows that 0·1 c.c. of the urine has digested 2 c.c. of a 0·1 per cent. solution of starch in half an hour at a temperature of 39° C.

Therefore 1 c.c. of urine will digest

$$0{\cdot}1 : 2 \text{ c.c. starch} :: 1 \text{ c.c.} : X.$$

This gives a diastase content of 20 units; in other words, 1 c.c. of the urine is capable of digesting 20 c.c. of a 0·1 per cent. solution of starch in half an hour, or, expressed symbolically,

$$d\left(\frac{39^\circ \text{ C.}}{30 \text{ min.}}\right) = 20 \text{ or } d = 20 \text{ units.}$$

In dealing with urines from cases of pancreatic disease the above method possesses many advantages, since the ten tubes give a wide range, and the differences are generally so large that minor errors of dilution, changes in volume of the urine, saline constituents, reaction, and presence of abnormal constituents have very little influence on the result. Thus we see how important it is to adopt a technique with freedom from any external sources of error, and any attempt to depart from this procedure either on the lines of simplification or amplification invariably meets with failure. After an extensive trial with this test on many hundreds of specimens of urine it has been possible to fix a standard for normal healthy individuals. The normal average value has been found to be 20 units, the maximum being 33·3 and the minimum 10 units, a sufficiently limited range from which to determine whether a given urine is normal or abnormal. The present paper deals with the use of this method for the diagnosis of diseases of the pancreas, where we expect to find an increase of diastase of such an extent that any sources of fallacy are promptly ruled out. Suffice it to say at this juncture that all possible fallacies have been considered, and since these apply more especially to the diagnosis of renal insufficiency they will not be given here. The results of these investigations have been already published in various papers by the writer dealing with acute nephritis as met with in France during the great war.

(*c*) *The Cammidge 'pancreatic' reaction.* The test devised by Cammidge over ten years ago has been the subject of considerable controversy, but we owe much to Cammidge for his laborious attempt to establish his test on a sound basis. Many workers have turned their attention to this test, and some still regard it as of value for diagnosis, but it has undoubtedly failed to fulfil the great expectations which were at first claimed for it. I myself carried out numerous examinations, and my colleague, Dr. Sladden, has already published his observations. In my opinion the test is of value as illustrating the phenomenon observed in my series of cases, namely, that many of these changes are of a 'fleeting character', appearing rapidly and just as quickly disappearing. The Cammidge test is time-consuming, and requires experience in carrying out the technique, and has no advantages over the estimation of the diastase in the urine. Consequently it has now been given up as a routine test in this hospital. The pathological interest of the test still remains, and it appears probable that the crystals obtained are in some way related to the presence of an abnormal amount of diastase in the urine. The new 'iodine coefficient' test has not been tried.

(*d*) *The Loewi adrenalin mydriasis test.* This test is one of great interest, and has the advantage of being easily applied. The principles on which it is based are at present a matter of controversy. The test depends upon the fact that adrenalin instilled into the conjunctival sac produces dilatation of the pupil in certain diseases, whereas in normal persons it has no such effect. One eye is selected, care being taken to exclude any evidence of corneal injury, ulceration, or inflammation. Into this eye two drops of a 1/1000 strength of adrenalin chloride are dropped, and the eye kept closed for a few minutes. The other eye is used as a control. After twenty minutes the eyes are again examined, and if the pupil of the experimental eye shows well-marked dilatation as compared with the control eye the test is regarded as positive. The maximum dilatation is attained in half an hour, and then rapidly disappears. The dilatation is often of quite a different type to that produced by mydriatic drugs, in that the pupil assumes an oval shape, the greatest diameter being either horizontal or vertical. The first time this test was tried was in the case of bronzed diabetes described later in this paper. The result was so striking that it stimulated interest in the test, and ensured its general application.

(*e*) *Glucose tolerance test.* The urine of all the cases included in this series was examined for the presence of sugar, and the results were in many cases of great interest. One case of acute pancreatitis when admitted to the ward showed well-marked glycosuria in a catheter specimen drawn off soon after the onset of an acute attack. The next specimen of urine excreted showed no trace of sugar, and all subsequent specimens were found to be free from sugar. Glycosuria of this sudden onset was found in other cases, and might frequently have been missed altogether. The occurrence, therefore, of glycosuria, especially when so rapid and transitory, is a phenomenon of no small interest, and coincides with the excretion of large amounts of diastase in the urine. These observations have been always uppermost in my mind in attempting to explain the association of the glycosuria, the diastase in the urine, and the Loewi reaction, especially their transitory characters. The presence of glycosuria affords valuable confirmatory evidence of pancreatic insufficiency, and if not present then the glucose tolerance test is tried. This test really consists in producing a type of alimentary glycosuria, and should be carried out with all due caution. A normal healthy individual is capable of absorbing 100 grm. of glucose without passing any abnormal amount of sugar in the urine. With 200 grm. of glucose there is nearly always a temporary glycosuria. The normal tolerance is actually found to be about 150 grm. The tolerance test consists in giving a person about 150 grm. of glucose dissolved in 300 c.c. of water on an empty stomach, and in such a form that it can all be consumed within a quarter of an hour. Whilst the test is being carried out the patient is kept on a milk diet, and usually the glucose is given in the morning of the second day of the diet. The urine is collected every hour after the glucose is given, each specimen being tested for sugar.

In cases where there is reason to suspect pancreatic insufficiency, a dose of

only 25 grm. is given for the first test, as there is the danger of putting too great a strain on the patient's tolerance with larger doses, which may lead to a persistent glycosuria. We can then test the tolerance to larger doses by stages if no glycosuria occurs. The occurrence of glycosuria after a dose of 25, 50, or 100 grm. of glucose does not necessarily imply that the pancreas is at fault, since disturbance of liver function and other diseases may yield similar evidence of lowered glucose tolerance. As a test, therefore, it simply serves as a useful guide, and the results should always be interpreted with due caution. Estimations of the blood-sugar content should also be made both before and at intervals after the administration of glucose by the mouth.

V. *The Value of the Methods used in certain selected Cases.*

To illustrate the value of the functional tests described in the preceding paragraph a brief note on a few selected cases is appended. They serve to show the extent of the inquiry and to supplement the records given in the tables.

Case I. The first case has already been fully described in this Journal, in a paper entitled 'A Contribution to the Study of Bronzed Diabetes', Jan., 1914, vii.

Case I. P. B., aged 44, a chemist and druggist by trade, was admitted under the care of Dr. A. E. Garrod on April 17, 1912, suffering from diabetes mellitus. On admission he was diagnosed as a case of bronzed diabetes, and a number of chemical tests were carried out during the course of the illness.

Summing up the results obtained the following tests suggested pancreatic insufficiency:

(1) Diastase in the urine.
(2) The occurrence of creatorrhoea (Schmidt's test).
(3) Loewi's adrenalin mydriasis test.
(4) Sahli's stearin capsule test.
(5) Lowered glucose tolerance and glycosuria.

The tests which did not support such a conclusion were:

(1) The absence of steatorrhoea.
(2) The normal tryptic and diastatic content of the faeces.
(3) The negative Cammidge 'pancreatic' reaction.
(4) The absence of oxaluria and indicanuria.

The pancreas at autopsy was found to be soft, misshapen by firm adhesions, and on section appeared of a deep brown colour. Histological examination showed well-marked fibrotic changes with abundant deposition of an iron-containing pigment.

Case II. W. D., aged 59, a carman by trade, was admitted to St. Bartholomew's Hospital on March 31, 1919, under the care of Sir Archibald Garrod, suffering from pain in the stomach and jaundice. His illness began December, 1918, with a feeling of weariness and fatigue. Two months later he was noticed to be yellow, but he had observed that his urine was dark in colour shortly before

this. At the same time he felt a dull aching pain across the upper part of the abdomen, especially after meals, which gradually became worse. There was no vomiting or constipation. The patient felt sure he had lost weight during the early months of 1919.

He had never suffered from jaundice before, but admitted he had been a very heavy spirit drinker before the advent of the war restrictions. On admission the patient appeared deeply jaundiced, with a soft, dry, and slightly irritable skin; soft enlarged glands were observed in the left supraclavicular fossa, but otherwise nothing of note was discovered in the chest. Examination of the abdomen revealed considerable enlargement of the liver, but the gall-bladder could not be felt. There was no ascites.

Rectal examination did not indicate any abnormality or growth in this region. The urine was of a dark brownish colour, acid in reaction, contained bile pigments, and gave a doubtful reduction with Fehling's test for sugar. The stools were clay coloured.

A diagnosis of carcinoma of the liver was made. About one week after admission sugar was definitely found in the urine, and the pancreas was at once placed under suspicion.

From this time onwards a complete investigation was made with a view to onfirming the presence of pancreatic involvement.

The urine contained sugar to the extent of 1·2 to 1·4 per cent., and maintained this amount during the whole course of the illness. Daily estimations were made on the twenty-four hourly samples, the total sugar ranging from a mere trace to 36 grm. There was no indicanuria, but large quantities of indoxyl glycuronates were excreted daily and frequently separated out as a blue sediment. This accorded with the absence of ethereal sulphates in the urine, a fact so frequently observed in cases of pancreatic insufficiency, and forms the subject of a separate inquiry by the writer. The presence of creatine in the urine was established, and was thought to indicate carcinoma of the liver. The daily variations in excretion of this substance were recorded, as also the effects of administration of creatine and creatinine by the mouth. A large number of observations have been made in this hospital, and these will form the subject of a separate communication. Suffice it to say at the moment that the presence of creatine in the urine is of no diagnostic value, and depends upon factors other than disease of the liver, which though fundamental are yet obscure.

The diastatic activity of the urine was estimated at intervals with the following results:

Date.	Volume of Urine in c.c.	Sugar. Total in Grm.	Diastase in Urine. Units.	Normal Diastase. Average Units.
April 15	1,000	12	125	16
„ 30	1,780	19·58	62·5	16
May 11	935	0·935	25	16
„ 18	2,180	15·26	32	16

The diastase content of the urine was abnormally high, but subsequently fell, although not to the normal level. This has been my experience of several similar cases, indicating that as the disease progresses the tendency is for the diastase to fall to normal or even below a normal value. Consequently in a case of long standing, or one where rapid destruction of pancreatic tissue has taken place, it may be difficult to draw any conclusion other than that the functions are seriously deranged. It bears no relation to the volume of the urine, or to the amount of sugar excreted.

Loewi adrenalin mydriasis test. This test was first tried on the left eye and gave a negative result. Subsequently it was found that the left pupil was not round, as in the right eye, but fixed by synechiae. When the test was tried on the right eye very definite dilatation was observed, and proved positive with

one exception. The test was applied on two consecutive days, and failed on the second day. After six days' interval the test was again positive. These observations are of great interest for two reasons: first, the importance of examining both eyes before carrying out the test, and secondly, the recognition that there is a definite fatigue period following the dilatation, during which period adrenalin ceases to have any effect. The clay-coloured stools were tested for urobilin and found to be negative, thus establishing the fact that no bile pigments were entering the intestine or, in other words, there was complete obstruction to the common bile duct.

The 'sajodin' test next occupied attention, the sajodin being given after breakfast in one single dose of 7½ grains. No iodides could be detected in the urine even for forty-eight hours after administration, whereas two normal healthy individuals excreted iodides within five to six hours after swallowing a similar dose. In view of the fact that no bile salts were entering the intestines this result is not surprising, and seriously militates against the practical utility of such a test.

Occult blood, the presence of which was detected by the benzidine test, was present on all occasions, care being taken to exclude any extraneous sources of blood or blood-products in the food. This finding was in my opinion very significant, since it established the fact that we were dealing with a malignant growth of the pancreas rather than a simple pancreatitis.

The faeces were examined on three occasions, and to emphasize the value of the results obtained I give them in tabular form:

Appearance.	April 17, Greyish White, Pasty.	April 26, White, Pasty Stool.	April 30, Clay-coloured, Oily.	Normal Values. Brown.
Reaction	acid	acid	acid	alk.
Urobilin	absent	absent	absent	+
Blood	present	present	present	0
Water		60·2	65·2	70–80
Total fat	67·8 %	71·0	70·0	15–25
Neutral fat	0·8 % } 28 %	56·6	59·0	10–15 { 1–2
Fatty acids	27·2 % }			9–13
Soaps	39·8	14·4	11·0	10–15
Ash	11·6	10·0	8·0	10–12
Microscopical:				
Muscle fibres	absent	absent	+ + + (nuclei)	+
Fat globules	a few seen	+	+ +	traces
Fatty acid crystals	+ +	+ +	+	0
Soaps	0	0	0	a few
Vegetable débris	+ +	+ +	+	+
Crystals	0	0	0	+
Diet	no meat	no meat	minced beef added	mixed diet

The results clearly justify the labour expended, since from the first analysis we should conclude that the changes present were largely biliary in origin. By taking into account the total fat values, however, a definite deduction can be drawn. In all cases of obstruction of the common bile duct without involvement of the pancreas, we never find the total fat value above 50 per cent., whereas in cases of pancreatic insufficiency figures much higher than this are the rule. The faeces in this case give evidence therefore of steatorrhoea, and the values for the different forms of fat show very clearly the gradual loss of fat-splitting powers as the disease progressed. In the last specimen examined there was a much

greater proportion of unsplit fat present than in the two previous specimens and a corresponding diminution in the amount of soaps.

Creatorrhoea. The simpler and much more efficient method of carrying out this test was adopted in preference to the original Schmidt test. The patient was given a diet containing no meat for several days, and one day at mid-day a quantity of under-cooked minced beef was administered. The stools were examined the following day, and showed abundant muscle-fibres with the characteristic striations, and even nuclei. This simple test can always be carried out and really embodies that of Schmidt and Kashiwado's modification of the same. The faeces examined on April 30, recorded in the table above, therefore demonstrate that there was well-marked creatorrhoea in this case. The patient suffered from severe abdominal pain and wasting, and died on June 11, 1919.

At the autopsy the pancreas was found to be hard and nodular, and almost entirely replaced by a malignant growth. The common bile duct was much distended and thin walled. The gall-bladder was much enlarged and bound down by adhesions to the liver, and this accounted for the fact that it was not palpable during life. The liver was much enlarged, but no obvious growth could be detected. On the upper surface of the left lobe several distended bile ducts could be seen. The whole of the liver and adjacent viscera, including the stomach, duodenum, and pancreas, were preserved entire, and will be dissected and described later. This case was interesting from many points of view, since all the tests applied pointed to disease of the pancreas, and the clinical diagnosis was as certain as it was possible to be in such a case.

Summing up the evidence in favour of pancreatic disease we have:

(1) The high diastase content of the urine.

(2) The occurrence of persistent glycosuria.

(3) The positive Loewi test.

(4) Well-marked and increasing steatorrhoea.

(5) Creatorrhoea.

(6) A positive sajodin test.

(7) The occurrence of occult blood in the stools.

(8) The absence of ethereal sulphates and indican, and their replacement by indoxyl glycuronates.

(9) The absence of urobilin in the faeces.

This case, therefore, illustrates the value of the application of particular laboratory methods, which, in the experience of the writer, have proved of the greatest value in assisting or confirming the diagnosis of pancreatic disease.

Case III. M. B., aged 50, a gas-worker by trade, was admitted to St. Bartholomew's Hospital on February 14, 1919, under the care of Dr. Langdon Brown, suffering from jaundice and pain in the stomach. Two months previously he had attacks of vomiting in the morning, and two weeks later abdominal pain, which was worse after food. He became yellow one week later. He had had no previous illnesses, but had been a heavy drinker, particularly of beer. His father died of 'cancer'.

On admission he had marked jaundice and pruritus, with a slow pulse and a soft systolic murmur at the apex of the heart. The liver was not uniformly enlarged, but a smooth elastic globular swelling was felt in the position of the gall-bladder. The urine contained bile pigments, but no bile salts, and gave a doubtful reduction with Fehling's test for sugar. The faeces showed a slight reaction for urobilin, and two tests for occult blood proved negative.

On February 21 the urine was systematically examined, but no sugar could be detected, the doubtful reduction of Fehling's test being probably due to the excess of bile pigment present.

The faeces examined the same day showed no trace of urobilin, muscle fibres were absent, and there was no excess of unsplit fat. Occult blood was again absent.

Faeces. The following results were obtained:

Appearance	Greyish coloured pasty stool
Odour	No definite rancid odour noticed
Reaction	Acid
Urobilin	Absent
Mucus	Traces only
Blood	Benzidine test negative
Microscopically:	No muscle fibres seen, elastic fibres absent
	Vegetable debris, present
	Fat globules, no excess
	Fatty acids, needles, abundant
	Starch, absent
	Crystals, absent

		Normal Values.
Total fat	= 63·36 per cent. of dried faeces	15–25
Neutral fat and fatty acids	= 11·6 " " " "	10–15
Combined fatty acids	= 52·7 " " " "	10–15
Organic matter	= 89·4 " " " "	85–89
Inorganic ash	= 10·6 " " " "	10–12

The results showed that the total fat was much higher than could be accounted for by simple obstruction to the common bile duct; in other words, there was steatorrhaea, and thus evidence of pancreatic insufficiency. The patient was on a meat-free diet, and this accounted for the absence of muscle fibres in the stools.

The diagnosis made was complete obstruction to the common bile duct, possibly due to a malignant growth. The diastase content of the urine amounted to 128 units, and the pancreas was, therefore, considered to be implicated.

As a result he was transferred to a surgical ward, and an exploratory operation was performed by Mr. Rawling on March 6. The common bile duct was found to be completely obstructed, but the nature of the obstruction could not be determined. The pancreas appeared to be enlarged and hard, and this change was considered to be inflammatory in origin. Drainage of the gall-bladder was carried out and the patient made an uninterrupted recovery. There was, however, a small permanent biliary fistula remaining, from which pure bile flowed, and the patient left the hospital provided with an instrument for the collection of the bile.

After the operation the following tests were carried out:

The diastase in the urine on May 20, over two months after the operation, had fallen to the normal value of 16 units, indicating that the pancreas was recovering its function.

Loewi's adrenalin mydriasis test was markedly positive on May 17, but proved negative one week afterwards.

The 'sajodin' test was negative, no iodides being found in the urine after the ingestion of 7½ grains of sajodin given in one dose.

Again, we have the test applied where there was evidence that no bile salts were entering the intestine, and therefore no real indication could be obtained as to whether the pancreatic secretion was also occluded from the intestine.

Occult blood. On a meat-free diet several separate tests were performed, and in every case a positive benzidine test occurred. This result pointed to some bleeding ulcerated surface in the gastro-intestinal tract, possibly from the obstructed common bile duct.

Creatorrhoea. On May 18 a meal of under-done minced beef was administered, and the faeces examined the following day. There was abundance of large well-striated muscle fibres, which when stained showed nuclei.

The diagnosis is still in doubt, but from the improvement in the patient's condition, it does not appear probable that the obstruction was due to a growth in the common bile duct. That there was chronic pancreatitis is beyond doubt, but this was probably secondary to what I believe to be an old ulcer situated in the duodenum close to the opening of the common bile duct and pancreatic duct.

The evidence for pancreatic insufficiency in this case is therefore provided by the following tests:

(1) High urinary diastase content early in the disease, later falling to normal.
(2) The presence of a high total fat content—more than 50 per cent.
(3) Creatorrhoea.
(4) Positive Loewi reaction.
(5) A positive sajodin test, absence of urobilin in the faeces.

The three selected cases above described represent the type of work involved, and express very clearly the main issue. Their number could be multiplied, but it is considered proper to the occasion to submit the remaining cases in tabular form. In the summary of cases printed at the end of the paper all the cases are grouped under the commoner classes of disease to which the pancreas is prone—acute pancreatitis, chronic pancreatitis, and malignant disease of the pancreas respectively. A group of cases of liver disease is included, as also some forms of intestinal diseases, and lastly cases of diabetes mellitus. In many of these patients complete analyses of the urine and faeces have been made, but these results have been excluded on account of the necessity of conserving space; they will be briefly discussed in the text.

Discussion of Results.

An excellent summary of our knowledge of the methods of diagnosis of pancreatic disease up to the year 1914 has been given by my colleague Dr. Sladden (15), who worked in my laboratory during 1913. This paper embodied in a critical review the present state of our knowledge with regard to

several of the functional tests mentioned in this paper. Under the circumstances it is unnecessary for me to dwell upon the conclusions of other writers, and the reader is referred to this paper for the information he may require. My present object is to detail my own personal experience of the various tests, gained as the result of several years' work upon the subject. The publication of these results was delayed by the war, although the greater part of the work was done in the pre-war period. In some ways this delay has been fortunate, since I have been able to apply my observations to two interesting cases since my return, and these are incorporated in the text in a description of selected cases. The clinical classification of diseases of the pancreas has been adopted, and it will be convenient to discuss the results under three headings: acute pancreatitis, chronic pancreatitis, and malignant disease of the pancreas.

Acute pancreatitis is a disease in which early diagnosis is of the greatest importance, consequently it is not possible to apply any tests which involve lengthy laboratory methods. In such cases an examination of the urine, tests for occult blood in the stools, microscopical examination of the faeces, and the Loewi test, are the only tests which can be carried out in the limited time allowed. Fortunately these tests have proved quite sufficient if one may judge from the tabulated series of cases below (No. I). By far the most important is the diastase content of the urine, and a fresh specimen of urine can generally be obtained, and the result completed within an hour. At the same time it is quite easy to do a Loewi test on the eye, and also to obtain a sample of the rectal contents by means of a plain water enema. The diastase content is almost invariably high, especially in the acute stages of the disease. When this stage has passed off the diastase content of the urine falls even to a normal value. The figures in the summary (No. I) illustrate this change. The fall may occur in a few hours, as for example an original diastase content of 200 units became 100 units the following day. The same 'fleeting' character is often found in the case of sugar in the urine. The most striking example was one case of acute pancreatitis where sugar was found in a catheter specimen of urine drawn off for diagnostic purposes, and subsequently the urine contained no sugar. The glycosuria, if present, may therefore last for only a few hours, a few days, or may persist for weeks, but sugar is not by any means constantly present in acute pancreatitis. The observations on the Loewi test are also of interest, since the positive results were obtained in those cases where there was a high diastase content of the urine, and also glycosuria. What a remarkable association! one which gives much food for thought and speculation. This association, which I describe as the 'tripod' tests, has never been described before, and from my series of cases I am inclined to regard it as of great importance. Apart from their value for diagnostic purposes these tests point the way to a possible solution of the problem of the exact function of the pancreas in controlling carbohydrate metabolism. The chief characteristic is their early manifestation, pointing to a sudden disturbance of some chemical mechanism. The close relation between the suprarenals and the pancreas, and the possibility of the

Loewi test being associated with the sympathetic nervous system, particularly the chromaffine portion of that system, has led me to devote my labours to this phase of the problem. A new method of estimating adrenalin and lipoids in the blood is at present under investigation. No quantitative proof has so far been forthcoming of the increased adrenalin content of the blood in pancreatic disease, although the observations of Pemberton and Sweet (16) on the influence of the adrenals over the pancreas are sufficiently striking to warrant such an investigation. These writers showed that intravenous injections of adrenalin, and of pituitary extract, inhibit the flow of pancreatic juice even after the blood pressure has returned to normal. The remarkable histological changes produced in the liver cells, particularly those lining the bile ducts, by repeated injections of adrenalin are well known to those observers who have worked on the causation of shock, and I have no doubt similar changes could be found in the pancreas, especially in the cells lining the ducts. The pancreas being thrown out of action is unable to balance the adrenalin secreted by the adrenals, and the blood receives an excessive amount of adrenalin—with the result that glycosuria occurs, and with it a rise in the diastase contents of the blood and urine, and a positive Loewi mydriasis test. Secretion of pancreatic juice is arrested, not through any deficiency of 'secretin', but through the excess of adrenalin in the blood. The obstruction to the flow of pancreatic juice leads to autolysis, with the resulting haemorrhage and fat necrosis. To complete the whole picture we want to know the adrenalin content of the blood, and this is my present objective. The examination of the faeces usually yields no conclusive evidence of pancreatic insufficiency in cases of acute pancreatitis, although the almost constant occurrence of occult blood is worthy of record. The Cammidge test was negative in three cases, but this has been the experience of a number of other workers, including Sladden (14). To sum up the results on acute pancreatitis, the association of glycosuria, an increased diastase in the urine far exceeding normal values, and a positive Loewi test afford very strong presumptive evidence of pancreatic involvement.

Passing now to the cases of inflammation of the pancreas of a more chronic type, one may refer to the record of twenty-eight cases recorded in the summary (No. II). Perhaps the most striking case was that of bronzed diabetes, where the pancreas was found to be completely cirrhosed at the autopsy. The following tests gave positive evidence of pancreatic insufficiency: Schmidt's test, Sahli's test, glycosuria, Loewi's adrenalin mydriasis test, and increased diastase in the urine. The Cammidge test, trypsin content of the faeces, diastase content of the faeces, and fat content of the stools were all negative. This case illustrates very well the true value of the tests as applied to any individual case. Reviewing all the results we find that there is no one test which is of absolute value in diagnosis. Creatorrhoea and steatorrhoea are of fairly common occurrence, but by no means constantly present, and the same applies to the Schmidt test and Kashiwado's modification when these were applied. A perusal of the summary will also show how frequently the Cammidge 'pancreatic' reaction was

negative, only one positive reaction being recorded in this series. The general urinary changes were not striking, and it cannot be said that urobilinuria, indicanuria, or oxaluria are in any way characteristic of pancreatic disease. The frequent association of a high diastase content of the urine, a positive Loewi mydriasis test, and the occurrence of glycosuria or a lowered glucose tolerance is again evident. The diastase values are not generally so high as those of acute pancreatitis, but one case stands apart—R. G., a clinically typical case of chronic pancreatitis. The diastase in the urine was 1,000 units, but after treatment fell to 50 units, and the patient eventually recovered. Another case showed 100 units, then 50 units, and after an interval of one year only 5 units. This patient died whilst I was abroad, but there is reason to suppose that his pancreas gradually lost its function, and eventually failed altogether. Associated with this high diastase was well-marked glycosuria and a positive Loewi. There were also creatorrhoea and steatorrhoea, as evidenced by repeated analysis of the stools. Another case, R. W., who had a permanent biliary fistula with chronic pancreatitis following upon an attack of acute cholecystitis, gave a diastase value of 100 units on three separate occasions, whilst the Loewi test was always negative, and therewas no glycosuria. There were, however, creatorrhoea and steatorrhoea. The case designated No. 3 in the group of selected cases described (Summary I) is of interest as illustrating the triple association, and also the temporary character of the tests. The diastase rapidly fell from 128 units to the normal value of 16 units, the glycosuria was also transient in character, and the Loewi test was changed from a positive to a negative mydriasis within an interval of one week. Here, again, there were creatorrhoea and steatorrhoea, but the latter was more characteristic of biliary obstruction rather than of actual pancreatic insufficiency. *The 'sajodin' test* was positive in so far as it represented both biliary and pancreatic insufficiency. The summary also shows several other cases of the same type sufficient to warrant a definite conclusion. It may be laid down that if these three tests are positive the pancreas is under grave suspicion, and the diagnosis is confirmed by the application of other tests of functional activity, more particularly the presence of creatorrhoea and steatorrhoea in the faeces. A most important point which is strongly emphasized in this work is early diagnosis, since the three cardinal tests may all be negative later, and the diagnosis left in doubt.

The diagnosis of pancreatic disease by means of these tests has frequently been the subject of controversy, and failures to obtain positive results have been rather the rule than the exception. I maintain that these observers have failed to realize their 'fleeting' nature, and have carried out the tests on cases where the disease has so far progressed as to leave no doubt as to the diagnosis, without the necessity of applying functional tests. A glance through the records of my series of cases will clearly demonstrate this, and it is with pleasure that corroboration of this work is to be found in a paper by Dr. Laurence Humphrey (17) of Cambridge, who reported two cases where the urinary diastase and the Loewi adrenalin mydriasis test were positive.

The same conclusions can be drawn from the series of cases of malignant disease of the pancreas (No. III). Case No. 2 becomes almost a complete experimental observation. The triple association is again to the fore. The glycosuria suddenly appeared one week after admission, and showed wide variations from a mere trace up to 30 grm. per diem. During the progress of the disease the diastase fell to a low level, and had the estimation been made in the later stages it would have been considered a negative result, and in consequence valueless from a diagnostic point of view. The results of the tests therefore were all in favour of pancreatic insufficiency, and the diagnosis made as certain as any clinical diagnosis could be, the ultimate proof being obtained at the autopsy. In passing, attention is called to the almost constant occurrence of occult blood in the stools, a phenomenon of some importance in differential diagnosis and treatment, since in the majority of cases of chronic pancreatitis no such evidence of haemorrhage in the intestinal tract is found.

The tests have been applied to a large number of cases of diseases of the liver, and particularly those where the pancreas has been under suspicion. The first case in the summary (No. IV) might almost be regarded as one of subacute pancreatitis, although no definite evidence was available at the time. Unfortunately the diastase estimation was not perfected at the time this patient was in hospital. The transitory Loewi test, and the temporary glycosuria together with steatorrhoea, are significant features in view of the results described above.

The other cases are of interest in demonstrating the low values for diastase compared with those in cases of pancreatic disease. Also the occasional occurrence of a positive Loewi test in three cases where the pancreas proved to be normal at the operation or autopsy. The results clearly show that it is not safe to dogmatize and to draw conclusions as to whether the pancreas is healthy or not on any one test. Taken by itself the Loewi test is almost valueless, since it is apt to lead to an entirely wrong conclusion. This in itself is to be regretted, since it is such a simple bedside test, and causes little inconvenience to the patient.

In the group classified under other diseases the type of case is of sufficient clinical interest to warrant a full discussion, but time and space will not admit of this in the present paper.

In the remarkable collection of cases of coeliac disease it will be noted that the diastase is always on the high side of normality, and there is frequently an associated steatorrhoea. Complete and definite evidence of any pancreatic insufficiency is, however, wanting, and with the present state of our knowledge of this disease such a conclusion is unjustifiable. No apology is made for including two cases of congenital steatorrhoea under this group. The valuable contribution of Garrod and Hurtley (18) on the subject is of great interest. Their case I was able to study subsequent to their publication, and could find no evidence of pancreatic insufficiency apart from the steatorrhoea. These cases, undoubtedly, belong to the class of inborn errors of metabolism, and the error is due to a congenital absence of steapsin or its precursor in the pancreatic juice.

Perhaps the most interesting group of cases are those of glycosuria, both temporary and permanent. The attempt to lay the blame upon the pancreas was the real and primary reason for this research. It has failed to incriminate the pancreas, not because that organ is free from disease, but because our tests for its lesions are inadequate. All the tests have so far proved negative, and in this connexion it is of interest to recall that Loewi introduced his test as one for diabetes mellitus. In my series the Loewi test has been consistently negative. The diastase content of the urine, contrary to all expectations, has been normal in every case. Further, all the tests for efficiency of the external secretion of the pancreas have yielded negative results in that no disturbance of functional activity has been found. Can it be that here again the tests are 'fleeting' in character and are missed because we do not see cases until the glycosuria or diabetes mellitus has become well established? A case of intermittent glycosuria, which I described in the St. Bartholomew's Hospital Reports with my colleague Dr. Roper (19), was thought to be an early case of diabetes mellitus. All the available tests for pancreatic insufficiency were applied, but with negative results. The conviction that the pancreas is the primary seat of disease in all cases of glycosuria and diabetes mellitus is gradually gaining ground, especially in the light of the recent work of Allen in America on diabetes mellitus. The results in my series serve to show that we are not yet on the right path to the solution of this problem, and until we know more of the part played by the pancreas in governing carbohydrate metabolism, and the interrelation of the ductless glands, our progress is necessarily slow.

In conclusion I would refer to the last seven cases recorded in the summary to illustrate the fallacies associated with certain tests, particularly the Loewi test. This test has been found positive in a variety of conditions where the pancreas is not obviously diseased. The outcome of the test therefore is that whilst advocating its general use it should be received with a healthy scepticism and freedom from bias. To discard it as a failure is unwarranted, and contrary to all the principles of clinical medicine, which advances when it takes cognizance of the collected data and carefully weighs all the evidence in the balance. The observations recorded in this paper are therefore sufficiently numerous and varied to show that no one test of pancreatic insufficiency is of value in the diagnosis of disease of that organ. Amongst all the tests so far devised I place three together as of the greatest value collectively. These are—(1) The diastase content of the urine and blood. (2) The Loewi adrenalin mydriasis test. (3) The occurrence of glycosuria, or a lowered glucose tolerance.

These three tests, it must be remembered, give results which are transitory in character, so that it does not follow that if all are negative there is no disease of the pancreas. If all three are positive then there is strong evidence sufficient to put the pancreas under suspicion. The diagnosis is confirmed if in association with these three tests we find creatorrhoea and steatorrhoea.

The ideal course is, undoubtedly, a complete survey of all the tests in every case, but one that is very rarely attained in this materialistic world, where the

old saying 'time is money' has received added force and meaning since the advent of the war.

Conclusions.

(1) To prove the individual and collective value of certain functional tests for the diagnosis of diseases of the pancreas has been the main object of this work.

(2) There is no one test so far devised which can be said to be pathognomonic of pancreatic insufficiency.

(3) The association of positive results in three tests, the increased diastase content of the urine, the Loewi adrenalin mydriasis test, and the presence of glycosuria, affords strong evidence that the pancreas is at fault.

(4) If there is in addition creatorrhoea and steatorrhoea, the suspicion of pancreatic insufficiency is confirmed.

(5) The transitory character of the phenomena which give positive results of diagnostic value must never be lost sight of when summarizing the evidence obtained from laboratory methods, and applying them to confirm or disprove the clinical diagnosis.

(6) The results of an investigation of cases of diabetes mellitus have been negative, in that the tests have not supplied any evidence of gross disturbance of pancreatic function in this disease.

(7) A review of the recorded cases reveals the fact that certain tests in their present form are of no value in the diagnosis of pancreatic disease, and should therefore be discarded. This applies more particularly to the methods of estimation of trypsin and diastase in the oil-test meal and faeces, the Sahli test, Kashiwado's modification of Schmidt's test, and the Cammidge 'pancreatic' reaction. To this list may be added the 'sajodin' test of Winternitz in view of its doubtful utility.

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Summary of Cases.

I. *Acute Pancreatitis.*

Case 1. H. B., male, aged 38. **Diagnosis:** Acute pancreatitis, fat necrosis, and acute nephritis. **Diastase in urine:** 200 units. **Loewi test:** positive. **Urine:** Glycosuria (increasing). Urobilin, indican, and calcium oxalate crystals absent. Cammidge test negative. **Remarks:** Glycosuria. 3-4 weeks before acute onset—patient died in coma.

Case 2. B. C., female, aged 57. **Diagnosis:** Acute haemorrhagic pancreatitis; fat necrosis. Operation: drainage of head of pancreas. **Diastase in urine:** Before operation, 200 units; after operation, 100 units. 2 years later, 128 units. **Loewi test:** Negative on three occasions. **Urine:** Sugar absent, acetoacetic acid present. Sugar present two years later. **Faeces:** Nil abnormal. Occult blood present. **Remarks:** Acute abdominal pain and vomiting. Patient recovered after operation. Exacerbation of acute pancreatitis two years later—sugar detected in the urine. Exploratory laparotomy. Patient still alive.

Case 3. S. B., male, aged 50. **Diagnosis:** Acute pancreatitis; duodenal ulcer. Operation. **Diastase in urine:** 128 units. **Loewi test:** negative. **Urine:** No sugar. **Faeces:** Occult blood present. **Remarks:** Abdominal pain. Patient left hospital improved.

Case 4. M. H. R., female, aged 50. **Diagnosis:** Acute pancreatitis; cirrhosis of liver. **Diastase in urine:** 222·2 units. **Loewi test:** positive. **Urine:** Urobilin present. Sugar absent. **Faeces:** Creatorrhoea; steatorrhoea. Occult blood present. **Remarks:** Abdominal pain, and vomiting followed by jaundice. Acute attack of pain and vomiting. Recovery.

Case 5. W. G., male, aged 50. **Diagnosis:** Acute haemorrhagic pancreatitis with fat necrosis. Operation and autopsy. **Diastase in urine:** 200 units. **Loewi test:** positive. **Urine:** Sugar detected on one occasion only. Cammidge test negative. **Faeces:** Steatorrhoea, but no creatorrhoea. Occult blood present. **Remarks:** Operation diagnosis confirmed at autopsy.

Case 6. F. M., male, aged 55. **Diagnosis:** Acute pancreatitis. Operation and autopsy. **Diastase in urine:** 200 units. **Loewi test:** positive. **Urine:** Sugar, urobilin, and albumin present. Cammidge test negative. **Faeces:** No steatorrhoea. Occult blood present. Fluid from drainage tube—no ferments detected. **Remarks:** At operation pancreas hard and enlarged, with extensive haemorrhages into it. Empyema of right side. At autopsy the pancreas was found to be gangrenous.

Case 7. J. W., male, aged 62. **Diagnosis:** Acute haemorrhagic pancreatitis; fat necrosis. Operation and autopsy. **Loewi test:** positive. **Urine:** Sugar present. **Remarks:** Operation: drainage of head of pancreas. Autopsy. The head and neck of the pancreas were haemorrhagic

and friable, with fat necrosis. Both the costal and diaphragmatic surfaces of the pleura also showed fat necrosis. There were two gall-stones present in the gall-bladder. *Trichina spiralis* was found in the skeletal muscles.

Case 8. A. P., female, aged 44. **Diagnosis**: Acute pancreatitis. **Diastase in urine**: 200 units (before operation), 100 units, then 50 units after operation. **Loewi test**: twice negative. **Urine**: Glycosuria. **Faeces**: No steatorrhoea. Urobilin present. Occult blood absent. **Remarks**: Operation—acute pancreatitis with fat necrosis, drainage of head of pancreas and gall-bladder. Recovery.

II. *Chronic Pancreatitis.*

Case 1. J. H., male, aged 43. **Diagnosis**: Obstructive jaundice; chronic pancreatitis. **Diastase in urine**: 100 units. **Loewi test**: negative. **Urine**: No sugar present. Bile pigments and albumin present. **Faeces**: Clay-coloured. **Remarks**: Patient recovered.

Case 2. G. M., male. **Diagnosis**: Chronic pancreatitis. **Diastase in urine**: 100 units, then 50, and 5 units one year later. **Loewi test**: positive. **Urine**: Persistent glycosuria and indicanuria. **Stools**: Clay-coloured; well-marked steatorrhoea and creatorrhoea. Occult blood absent. **Remarks**: Chronic pancreatitis of long standing with much wasting. Died.

Case 3. R. W., male, aged 47. **Diagnosis**: Acute cholecystitis, chronic pancreatitis. Operation. **Diastase in urine**: 100 units on three occasions. **Loewi test**: negative on three occasions. **Urine**: No glycosuria; urobilinuria present. **Faeces**: Well-marked steatorrhoea and creatorrhoea. Occult blood, negative. **Remarks**: A permanent biliary fistula present. Patient died two years after operation—much wasting.

Case 4. J. H. P., male. **Diagnosis**: Chronic pancreatitis. **Urine**: Glycosuria. Cammidge test negative. **Faeces**: Well-marked steatorrhoea. Occult blood absent. **Remarks**: A case showing clinically chronic pancreatitis of long standing.

Case 5. H., female. **Diagnosis**: Chronic pancreatitis. **Urine**: Sugar absent. Cammidge test negative. **Faeces**: Steatorrhoea. Creatorrhoea. Occult blood absent. **Remarks**: An old case diagnosed by the appearance and character of the stools.

Case 6. N., male. **Diagnosis**: Chronic pancreatitis. Operation. **Urine**: Cammidge test negative. **Faeces**: Steatorrhoea and creatorrhoea. Occult blood absent. **Remarks**: Recovery.

Case 7. P. C., male. **Diagnosis**: Chronic pancreatitis? Carcinoma of head of pancreas. Operation. **Urine**: No glycosuria; indicanuria present. Cammidge test negative. **Faeces**: Creatorrhoea, but no steatorrhoea. **Remarks**: Recovered. The possibility of the hard pancreas found at operation being inflammatory in nature was considered.

Case 8. J. B. J., male, aged 47. **Diagnosis**: Chronic pancreatitis; persistent diarrhoea. **Diastase in Urine**: 50 units. **Faeces**: Steatorrhoea and creatorrhoea, also starch granules. **Remarks**: Discharged from hospital, and died shortly afterwards.

Case 9. J. T., male, aged 60. **Diagnosis**: Chronic pancreatitis; pyloric obstruction. Operation. **Loewi test**: negative. **Urine**: No sugar; indicanuria present. Cammidge test negative. **Faeces**: No abnormality discovered. **Test meal**: showed slight hyperchlorhydria. **Remarks**: After operation patient recovered. The pancreas was found to be hard and enlarged.

Case 10. L. J., female. **Diagnosis**: Chronic pancreatitis. Operation. **Diastase in urine**: 22·2 units, after operation 10 units. **Loewi test**: negative. **Urine**: Sugar present, but later disappeared; traces of albumin. **Blood sugar**: 0·170 grm. per cent. **Remarks**: A hard pancreas found. No gall-stones felt.

Case 11. C. C., female, aged 54. **Diagnosis**: Cirrhosis of liver. ?Chronic pancreatitis. No operation. **Loewi test**: negative. **Urine**: No glycosuria; indicanuria present. Cammidge test negative. **Faeces**: Clay-coloured. Schmidt-Kashiwado test. Negative. **Remarks**: Jaundice and abdominal pain. Discharged improved.

Case 12. H. T., male, aged 29. **Diagnosis**: Chronic diarrhoea, six months' history. **Diastase in urine**: 200 and 250 units. **Loewi test**: positive (twice). **Urine**: No glycosuria. Cammidge test negative. **Faeces**: No excess of fat. **Remarks**: Patient improved on

pankreon, and left hospital. There was a lowered glucose tolerance and steatorrhoea after a diet rich in fat, and the oil-test meal showed a diminished tryptic activity.

Case 13. C. K., female, aged 40. **Diagnosis**: Recurring jaundice. Chronic duodenal ulcer with adhesions probably involving the pancreas. **Loewi test**: positive. **Urine**: No glycosuria. Cammidge test negative. **Faeces**: No excess of fat. **Remarks**: There was the possibility of slight chronic pancreatitis in this case, but not proven.

Case 14. S., female. **Diagnosis**: Chronic pancreatitis. **Diastase in urine**: 300 units. **Loewi test**: positive. **Urine**: Sugar present, and persisted. **Remarks**: Severe abdominal pain, much wasting. Died in three months from wasting and exhaustion.

Case 15. P., male, aged 50. **Diagnosis**: Chronic pancreatitis. Operation. **Diastase in urine**: 50 units. **Loewi test**: positive. **Urine**: Glycosuria. **Faeces**: Steatorrhoea and creatorrhoea. Occult blood absent. **Remarks**: Diagnosed by operation, and died subsequently in an infirmary.

Case 16. Male. **Diagnosis**: Chronic pancreatitis. **Diastase in urine**: 1,000 units, then 50 units, finally 25 units three months later. **Urine**: No glycosuria, no ethereal sulphates. **Faeces**: Steatorrhoea. No occult blood. **Remarks**: No operation, but clinically a typical case of chronic pancreatitis.

Case 17. C. B., male, aged 46. **Diagnosis**: Obstruction to common bile duct. ? Chronic pancreatitis. ? Carcinoma of head of pancreas. Operation. **Diastase in urine**: 50 units. **Urine**: Sugar absent, bile pigments present. **Faeces**: Clay-coloured. Fat content of biliary type. **Remarks**: Cholecystoduodenostomy in 1914. Pancreas found to be hard and enlarged. Alive in 1917, but complained of abdominal pain, and a lump could be felt in the region of the pancreas.

Case 18. K. D., female, aged 37. **Diagnosis**: Appendix abscess. General pelvic inflammation. **Diastase in urine**: 100 units. **Loewi test**: negative. **Urine**: Glycosuria one day only. **Remarks**: Operation appendicectomy. Pancreas under suspicion.

Case 19. E. E., female, aged 58. **Diagnosis**: Obstructive jaundice. Chronic pancreatitis. **Urine**: Sugar absent. Cammidge test positive. No oxalate crystals. **Faeces**: Clay-coloured, urobilin absent, no steatorrhoea. **Remarks**: Gall-stones removed 10 years previously. Operation for cholecystostomy, and pancreas found to be hard.

Case 20. W. B., male, aged 36. **Diagnosis**: Cirrhosis of liver. Hepatitis. ? Chronic pancreatitis. **Diastase in urine**: 33·3 units. **Loewi test**: positive, but twice negative later. **Urine**: No glycosuria. Cammidge test negative. **Faeces**: Nil abnormal found. No steatorrhoea. Occult blood absent. **Remarks**: A lowered glucose tolerance was observed, but no laevulosuria followed the administration of 25 grams.

Case 21. D. T., male, aged 56. **Diagnosis**: Chronic pancreatitis; glycosuria. **Diastase in urine**: 50 units. **Loewi test**: positive. **Urine**: Glycosuria present, indicanuria present. **Faeces**: Steatorrhoea. Urobilin present. Occult blood absent. **Remarks**: History of wasting, epigastric pain, pain in the back and in right shoulder, and the passage of fatty stools.

Case 22. B. L. C., male, aged 40. **Diagnosis**: Chronic pancreatitis. **Diastase in urine**: 100 units. **Urine**: No glycosuria. **Faeces**: Normal. **Remarks**: Operation 8 years previously, and chronic pancreatitis found. Attacks of acid gastric dyspepsia since. No hyperglycaemia found.

Case 23. E. C., female, aged 58. **Diagnosis**: Chronic pancreatitis; obstructive jaundice. **Urine**: Sugar absent. Cammidge test positive. **Faeces**: Clay-coloured; urobilin absent. No excess of fat found. **Remarks**: 10 years previously operation for removal of gall-stones, and pancreas found to be hard.

Case 24. T. L., male. **Diagnosis**: Chronic pancreatitis. **Diastase in urine**: 50 units. **Loewi test**: positive. **Urine**: No glycosuria. **Faeces**: Steatorrhoea. Urobilin present. **Remarks**: Operation; also long history of the passage of fatty stools.

Case 25. M. R., female, aged 40. **Diagnosis**: Retroperitoneal haemorrhage. Operation. Post-operative pancreatitis. **Diastase in urine**: 33·3 units (2 days before operation), 50 units (4 days after operation). **Loewi test**: negative. **Urine**: No glycosuria. **Faeces**: Occult blood present. **Remarks**: Operation. No cause for haemorrhage found. Pancreas appeared normal, but incised, and drainage of head of pancreas. No fat necrosis. Recovered.

Case 26. S. B. male, aged 50. **Diagnosis**: Chronic pancreatitis. Duodenal ulcer.

Diastase in urine: 128 units. **Loewi test**: negative. **Urine**: No glycosuria. **Faeces**: Occult blood present. **Remarks**: Abdominal pain of 2 years' duration. Operation.

Case 27. S. P., male, aged 50. **Diagnosis**: General peritonitis. **Diastase in urine**: 100 units on two occasions. **Loewi test**: positive on both eyes. **Urine**: No glycosuria, but urobilinuria and indicanuria present. **Remarks**: Operation and autopsy. Pancreas appeared normal macroscopically. General peritonitis with adhesions found.

Case 28. D. G., female, aged 58. **Diagnosis**: Cholelithiasis; secondary pancreatitis. **Loewi test**: positive during jaundice, negative later. **Urine**: Glycosuria and urobilinuria. **Faeces**: Steatorrhoea. Total fat 60·5 per cent. Occult blood absent. **Remarks**: Improvement followed disappearance of jaundice.

Carcinoma of Head of Pancreas.

Case 1. C. N., male, aged 50. **Diagnosis**: Carcinoma of head of pancreas. Generalized secondary growths. **Diastase in urine**: 200 units. **Loewi test**: positive. **Urine**: Persistent glycosuria. Bile pigments present. **Faeces**: Creatorrhoea and steatorrhoea. Occult blood present. **Test meal**: Normal values for gastric contents. **Remarks**: Pancreas found at operation to be involved in a new growth. At autopsy the pancreas was apparently almost entirely replaced by new growth. There was an enlarged liver, venous thrombosis, and ascites.

Case 2. H. H., male, aged 50. **Diagnosis**: Carcinoma of stomach, adherent to pancreas. **Diastase in urine**: 100 units. **Loewi test**: negative. **Urine**: No glycosuria. **Faeces**: No occult blood, but definite melaena later. **Blood**: Blood-sugar 0·12 grm. per cent. **Remarks**: Operation. Discharged I. S. Q.

Case 3. E. H. F., male, aged 60. **Diagnosis**: Carcinoma of ampulla of Vater. Interstitial hepatitis. **Diastase in urine**: 100 units. **Urine**: No glycosuria. Bile pigments present. **Remarks**: Abdominal pain and jaundice, with enlarged liver. Autopsy. Pancreas appeared normal. Growth proved to be a columnar-celled carcinoma.

Case 4. M. A. C., female, aged 62. **Diagnosis**: Carcinoma of pylorus involving head of pancreas. **Urine**: No glycosuria, no oxaluria. Cammidge test negative. **Remarks**: The pancreas at autopsy showed chronic inflammatory changes only.

Case 5. C. H., male, aged 53. **Diagnosis**: Carcinoma of head of pancreas. **Diastase in urine**: 50 units. **Loewi test**: positive. **Urine**: Bile pigments present, no glycosuria. **Faeces**: No steatorrhoea, no urobilin. Occult blood absent. **Remarks**: Jaundice, enlarged liver and gall-bladder. Operation. Enlarged head of pancreas, distended common bile duct, no stones felt. Cholecystenterostomy performed. Autopsy. Hard pancreas infiltrated with columnar-celled carcinoma. Stricture of common bile duct found, probably primary growth.

Diseases of the Liver.

Case 1. T. D., male, aged 24. **Diagnosis**: Cirrhosis of liver. Chronic peritonitis. **Diastase in urine**: 10 units. **Urine**: Urobilinuria, no bile pigments or bile salts. **Faeces**: Nil abnormal. **Remarks**: At autopsy, cirrhosis of liver, chronic peritonitis, enlarged spleen, ascites. Pancreas normal.

Case 2. J. R., female, aged 45. **Diagnosis**: Cirrhosis of liver. Gall-stone in cystic duct. Streptococcal septicaemia. **Diastase in urine**: 10 units. **Urine**: Bile pigments present. **Faeces**: Pale-coloured stools, no steatorrhoea, urobilin present. **Remarks**: Ascites; diastase in ascitic fluid=10 units; lipase content, normal. Autopsy.

Case 3. C. C., male, aged 67. **Diagnosis**: Cirrhosis of liver. Recurring haemorrhagic ascites. **Diastase in urine**: 25 units. **Loewi test**: negative. **Urine**: No glycosuria. **Remarks**: Lowered glucose tolerance, between 25 and 50 grm. Autopsy.

Case 4. E. B. **Diagnosis**: Catarrhal jaundice. **Diastase in urine**: 50 units. **Loewi test**: negative. **Urine**: No glycosuria. **Remarks**: Jaundice disappeared with treatment.

Case 5. J. S., female, aged 49. **Diagnosis**: Catarrhal jaundice. **Diastase in urine**: 10 units. **Urine**: No glycosuria. **Remarks**: At operation, no cause for jaundice discovered.

Case 6. J. B., male, aged 37. **Diagnosis**: Transitory jaundice with transitory ascites. **Diastase in urine**: 33·3 units. **Loewi test**: negative. **Urine**: Urobilinuria. No glycosuria. Traces of bile pigment, no bile salts. **Remarks**: Patient cured.

Case 7. F. J., female, aged 20. **Diagnosis**: Catarrhal jaundice. **Diastase in urine**: 33·3 units. **Urine**: No glycosuria. Urobilin present. **Remarks**: Jaundice, vomiting, and constipation. Cured.

Case 8. F., male, aged 55. **Diagnosis**: Transient jaundice with intermittent pyrexia. **Diastase in urine**: 32 units. **Faeces**: No steatorrhoea. Occult blood absent. **Remarks**: Discharged I. S. Q.

Case 9. K. H., female, aged 74. **Diagnosis**: Obstruction of common bile duct by tumour. Gastric ulcer and cholangitis. **Loewi test**: negative. **Urine**: Bile pigments. No glycosuria. Cammidge test negative. **Faeces**: Clay-coloured stools, urobilin absent. **Remarks**: Autopsy. Pancreas normal on section. Gastric ulcer showed inflammatory changes and also new growth.

Case 10. E. N., female, aged 39. **Diagnosis**: Empyema of gall-bladder. **Urine**: No glycosuria. Urobilinuria and indicanuria well marked. Cammidge test negative. **Faeces**: No steatorrhoea. Urobilin present. Occult blood absent. **Test meal**: Normal values. **Remarks**: Operation: incision and drainage of gall-bladder. There was no lowered glucose tolerance. Sahli test positive.

Case 11. W. B., male, aged 61. **Diagnosis**: Jaundice. Enlarged liver and spleen. Adherent pericardium. **Diastase in urine**: 50 units (highly concentrated urine). **Urine**: Bile pigments and traces of albumin present. **Faeces**: Clay-coloured, no steatorrhoea. Occult blood absent. **Remarks**: At autopsy pancreas proved to be normal.

Case 12. R. W., female, aged 37. **Diagnosis**: Enlarged liver, ascites, glycosuria. **Diastase in urine**: 8 units. **Loewi test**: negative. **Urine**: Glycosuria. **Faeces**: No steatorrhoea. Occult blood absent. **Remarks**: Operation two years previously, diagnosis of new growth of liver made.

Case 13. K. C., female, aged 42. **Diagnosis**: Cirrhosis of liver. **Diastase in urine**: 33·3 units. **Urine**: Bile pigments present. **Faeces**: Clay-coloured, no steatorrhoea. Urobilin present. **Remarks**: Operation: cholecystostomy. Autopsy. No enlargement of liver or gall-bladder; pancreas normal.

Case 14. E. A., female, aged 52. **Diagnosis**: Intermittent jaundice. Perihepatitis; enlarged spleen. **Diastase in urine**: 22·2 units. **Loewi test**: negative. **Urine**: No glycosuria, but bile pigments present. **Faeces**: Pale-coloured stools, no steatorrhoea. Urobilin present. **Remarks**: Liver found to be dark coloured and lobulated, and the spleen enlarged.

Case 15. M. D., female, aged 25. **Diagnosis**: Jaundice. **Diastase in urine**: 50 units. **Loewi test**: positive. **Urine**: No glycosuria, but bile pigments and acetone bodies present. **Remarks**: Abdominal pain, vomiting, jaundice. Operation; no cause found, and pancreas appeared normal.

Case 16. J. E., male, aged 70. **Diagnosis**: Jaundice, biliary colic. **Diastase in urine**: 33·3 units. **Loewi test**: positive. **Urine**: Bile pigments present. **Faeces**: No occult blood. **Test meal**: No free hydrochloric acid present. **Remarks**: Loss of weight, and vomiting. Operation; no cause found, and pancreas appeared normal.

Case 17. T. M., male, aged 68. **Diagnosis**: Carcinoma of liver. Occlusion of bile passages; old pleural and peritoneal adhesions. **Diastase in urine**: 20 units. **Loewi test**: positive. **Urine**: No glycosuria. **Faeces**: Clay-coloured. **Remarks**: At autopsy no primary lesion found; pancreas normal.

Case 18. B., male. **Diagnosis**: Carcinoma of liver and bronchial glands, also deposits in ribs. Chronic interstitial nephritis. **Diastase in urine**: 33·3 units. **Urine**: Glycosuria. Traces of albumin. **Blood**: Sugar content = 0·22 grm. per cent. **Remarks**: Autopsy. The pancreas showed numerous small patches like fat necrosis which had become fibrosed.

Case 19. E., male, aged 67. **Diagnosis**: Carcinoma of gall-bladder or ducts. Secondary deposits in liver. **Diastase in urine**: 50 units. **Loewi test**: negative. **Remarks**: Clinical diagnosis; no autopsy allowed.

Case 20. J. H., male. **Diagnosis**: Carcinoma of liver. **Diastase in urine**: 16 units. **Urine**: Bile pigments present. **Faeces**: Pale-coloured, pasty stools, showing excess of fatty acids and traces of urobilin.

Other Diseases.

Case 1. R. W., female, aged 5. **Diagnosis**: Coeliac disease. **Diastase in urine**: 50 units, then 33·3 units. **Urine**: No glycosuria. **Faeces**: Typical pale-coloured fatty stool, showing excess of fatty acids.

Case 2. E. G., male, aged 3. **Diagnosis**: Coeliac disease. **Diastase in urine**: 32 units. **Loewi test**: negative. **Urine**: No glycosuria. **Faeces**: Steatorrhoea, with excess of fatty acids. Urobilin absent. Occult blood absent.

Case 3. S. W., female, aged 5. **Diagnosis**: Coeliac disease. **Diastase in urine**: 50 units. **Faeces**: Steatorrhoea. Urobilin present. Occult blood absent.

Case 4. G. P., male, aged 12. **Diagnosis**: Coeliac disease. **Diastase in urine**: 25 units. **Loewi test**: negative. **Faeces**: Pale-coloured frothy stool. Urobilin present. No steatorrhoea. **Remarks**: Abdominal pain, constipation, and pallor; distended and resonant abdomen; died; autopsy.

Case 5. F., female, 18 months. **Diagnosis**: Coeliac disease. **Diastase in urine**: 50 units. **Urine**: No glycosuria. **Faeces**: Pale-coloured stool, showing excess of fatty acids. Urobilin present in traces. No occult blood.

Case 6. T., female, aged 18 months. **Diagnosis**: Coeliac disease. **Diastase in urine**: 20 units. **Urine**: Sugar absent. **Faeces**: Pale-coloured stool, showing excess of fatty acids. No occult blood.

Case 7. H. C., male, aged 6 years. **Diagnosis**: Congenital steatorrhoea. **Diastase in urine**: 10 units. **Loewi test**: negative. **Urine**: No glycosuria. Cammidge test positive. **Faeces**: Excess of undigested fat. **Remarks**: Case fully described by Garrod and Hurtley. Seen nine years later, and tests applied, but no evidence of pancreatic insufficiency found apart from the steatorrhoea.

Case 8. E., male, aged 2 years. **Diagnosis**: Congenital steatorrhoea. **Diastase in urine**: 25 units. **Loewi test**: negative. **Urine**: No glycosuria. **Faeces**: Steatorrhoea.

Case 9. A. P., female, aged 17. **Diagnosis**: Diabetes mellitus. **Loewi test**: negative. **Urine**: Glycosuria. Cammidge test negative. Sahli test negative. **Remarks**: At autopsy the pancreas appeared small, but otherwise no abnormality could be discovered either macroscopically or microscopically.

Case 10. Female. **Diagnosis**: Diabetes mellitus. **Diastase in urine**: 10 units. **Urine**: Glycosuria. **Faeces**: No steatorrhoea. Urobilin present. **Remarks**: Died in diabetic coma.

Case 11. J. B., female, aged 7 years. **Diagnosis**: Diabetes mellitus. **Diastase in urine**: 33·3 units. **Urine**: Glycosuria. **Faeces**: No steatorrhoea. Urobilin present. **Remarks**: Died in diabetic coma.

Case 12. D. W., male, aged 33. **Diagnosis**: Transient glycosuria. **Loewi test**: negative. **Urine**: Glycosuria. Cammidge test negative. Glucose tolerance test showed a lowered glucose tolerance. **Remarks**: Slight restriction of carbohydrates in the diet removed the glycosuria. There was a history of duodenal ulcer two years previously.

Case 13. J. C., male, aged 44. **Diagnosis**: Diabetes mellitus. **Urine**: Cammidge test negative. **Faeces**: No steatorrhoea.

Case 14. R. M., male, aged 19. **Diagnosis**: Intermittent glycosuria. **Urine**: Glycosuria. Cammidge test negative. **Faeces**: No steatorrhoea. No occult blood. **Remarks**: No evidence of pancreatic origin of the glycosuria could be ascertained. When the glycosuria disappeared the patient tolerated 50 and 100 grm. of glucose without any signs of glycosuria.

Case 15. A. M., female, aged 33. **Diagnosis**: Glycosuria. **Urine**: Well-marked glycosuria. Cammidge test negative. **Faeces**: No steatorrhoea. **Remarks**: No evidence of pancreatic insufficiency obtained.

Case 16. S. B., male, aged 52. **Diagnosis**: Diabetes mellitus. **Diastase in urine**: 50 units (volume of urine 2,700 c.c. for twenty-four hours). **Loewi test**: negative. **Urine**: Glycosuria. **Remarks**: Improved on dieting.

Case 17. F., female. **Diagnosis**: Diabetes mellitus. **Diastase in urine**: 10 units. **Loewi test**: negative. **Urine**: Glycosuria.

Case 18. J. W. A., male, aged 29. **Diagnosis**: Diabetes mellitus. **Diastase in urine**: 10 units. **Urine**: Sugar present. **Blood**: Sugar content = 0·37 grm. per cent. **Remarks**: History of two years' duration of glycosuria. Signs of diabetic coma.

Case 19. A. C. M., female. **Diagnosis**: Glycosuria. **Diastase in urine**: 22·2 units. **Loewi test**: negative. **Urine**: Sugar present three years previously, now absent. **Faeces**: Steatorrhoea. Occult blood present. **Test meal**: Hyperchlorhydria. **Remarks**: Epigastric pain. X-ray examination showed great distension of duodenum. The case was regarded as one of gastric ulcer and the pancreas under suspicion.

Case 20. C. C., male, aged 59. **Diagnosis**: Glycosuria. **Diastase in urine**: 25 units. **Loewi test**: negative. **Urine**: Sugar present. **Remarks**: Loss of weight, 15–8 stones, and possibility of pancreatic origin of glycosuria considered.

Case 21. H. J. H. S., male, aged 31. **Diagnosis**: Glycosuria. **Diastase in urine**: 50 units. **Loewi test**: negative. **Urine**: Pronounced glycosuria two years previously, now absent. Normal sugar tolerance. **Remarks**: Loss of weight. Pancreatic origin of the glycosuria considered.

Case 22. D. C. D., male. **Diagnosis**: Glycosuria. **Diastase in urine**: 25 units. **Loewi test**: negative. **Urine**: Glycosuria. **Remarks**: The glycosuria gradually disappeared on dietetic treatment.

Case 23. D. B., male. **Diagnosis**: Glycosuria and jaundice. **Diastase in urine**: 33·3 units. **Loewi test**: negative. **Urine**: Glycosuria. **Faeces**: No steatorrhoea. Urobilin present. **Remarks**: Jaundice disappeared, but glycosuria persisted.

Case 24. F., female, aged 16. **Diagnosis**: Chronic colitis. **Diastase in urine**: 10 units. **Loewi test**: positive, but later negative. **Urine**: Sugar absent. **Faeces**: Pale-coloured stools, showing excess of fatty acids. **Remarks**: Infantilism ? pancreatic.

Case 25. G. E., male, aged 49. **Diagnosis**: Abdominal pain, wasting. **Diastase in urine**: 20 units. **Urine**: Sugar absent. **Faeces**: Pale-coloured, but no steatorrhoea. Urobilin present. **Remarks**: Loss of weight, 11–9 stones. Diarrhoea. No cause discovered.

Case 26. E. A., female, aged 11. **Diagnosis**: Anorexia nervosa. **Loewi test**: negative. **Urine**: Sugar absent. Cammidge test negative. **Faeces**: No steatorrhoea. No occult blood. **Remarks**: Wasting, improvement on dieting.

Case 27. H. F., male, aged 54. **Diagnosis**: Carcinoma of pylorus. **Loewi test**: positive, later negative. **Urine**: No sugar. Cammidge test positive. **Faeces**: No steatorrhoea. **Test meal**: Suggested malignant disease of the stomach. Kashiwado's test negative. **Remarks**: At operation and autopsy the pancreas was found to be normal.

Case 28. W. P., male, aged 39. **Diagnosis**: Dilatation of stomach. **Loewi test**: negative. **Urine**: No glycosuria. Cammidge test negative. **Faeces**: No steatorrhoea. Occult blood present. **Remarks**: No cause for the dilatation of the stomach discovered. Improved after gastro-enterostomy.

Case 29. E. S., female, aged 63. **Diagnosis**: Carcinoma of left breast. Secondary deposits in pituitary, pineal, and suprarenal glands. **Diastase in urine**: 10 units. **Urine**: No glycosuria. **Faeces**: No steatorrhoea. Urobilin present. **Remarks**: The pancreas appeared normal both macroscopically and microscopically. This result is of interest in view of the involvements of the other ductless glands.

Case 30. A. W., female, aged 45. **Diagnosis**: Carcinoma of the breast. Bronchitis. **Urine**: Sugar absent. Cammidge test negative. **Faeces**: No steatorrhoea. Sahli test negative. **Test meal**: Normal values. **Remarks**: No evidence of involvement of the pancreas.

Case 31. H. H., male, aged 50. **Diagnosis**: Carcinoma of testis. Secondary deposits in lumbar glands. **Diastase in urine**: 33·3 units. **Loewi test**: negative. **Urine**: No glycosuria. **Faeces**: No steatorrhoea. **Remarks**: Large haemorrhagic tumour in epigastrium, thought to be pancreatic at operation, but at autopsy the pancreas proved to be normal.

THE EFFECT OF HIGH PROTEIN DIET ON ALBUMINURIA AND BLOOD UREA IN CASES OF NEPHRITIS

By E. WORDLEY

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THESE observations were undertaken to ascertain whether the excretion of protein in the urine in persons suffering from renal disease had any relation to the amount of protein in the diet. It is often stated that a rich protein diet is harmful in chronic renal disease, and if persisted in, leads to an increase in the albuminuria. Assuming that the lesion is stationary and not progressive, and that the excretory functions of the kidneys are normal, it is difficult to see how this should be so unless the foreign protein is taken in such enormous quantities as to be excreted unchanged. In the following experiments all classes of renal disease were used, but, of course, before deciding on a satisfactory diet for a patient, it is important to know whether the lesion is stationary, and whether the excretory powers of the kidney are normal. Until recently this was a difficult matter. We knew that oedema was evidence of a deficiently acting kidney, and that such cases showed an inability to excrete chlorides. The case in which it was difficult to ascertain the condition of the kidneys was the *parenchymatous* type in which the albuminuria was present, but the oedema had long since passed away. Many such cases, in time, became obvious types of chronic *interstitial* nephritis, with definite symptoms of serious renal damage. High blood-pressure, to take one of these symptoms, is obviously a sign of disease, and is associated with chronic kidney lesions of a severe kind. The distinction between cases of pure high blood-pressure—Clifford Allbutt's hyperpiesia (1)—and early interstitial nephritis has often been difficult to make with tests of renal function, but Maclean's urea test (7) is of the greatest value in these cases, and appears to be the most efficient and the easiest method of differentiation we have. Two illustrative cases of high blood-pressure, without serious kidney failure, are included amongst the cases described later. As is well known, it is generally accepted that a rich protein diet is of value in the treatment of certain chronic cases with persistent oedema, on the ground that the plasma protein, being low, will be increased thereby (2). Maclean has shown that, in many cases at least, this is not so, and that in spite of a rich protein diet the plasma protein remains the same (3); he suggests that the beneficial effect of such a diet is

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to raise the urea content of the blood, thus inducing a diuresis. Further, he points out that often the case with intense oedema shows no tendency to urea retention, so that the blood urea may be raised with safety, and the amount of protein excreted in the urine may be ignored (4). Since it may be inadvisable to raise the blood urea in some cases, each case should be investigated to settle this point. For this purpose the urea content of the blood may be estimated, and this test has been used for some considerable time. The blood urea, however, varies very considerably with the diet, and under certain circumstances may be within almost normal limits in persons with very damaged kidneys if the diet is low in protein. Instances are given later in which the uraemic symptoms started in spite of the blood urea being practically normal. In Maclean's urea test, however, we have a most delicate and efficient method which, whatever the blood urea may be, will show instantly any variation in the ability of the kidneys to concentrate urea.

In one case noted later, the plasma protein was low throughout, although no oedema was present, which seems to be an additional fact against the view that a low protein content of the blood in the hydraemic type of case accounts for the oedema.

It would seem, therefore, rational to give a rich protein diet in all cases where there is no evidence of retention of urea in the blood. Herringham (5) quotes figures to show that a rich protein diet gives rise to no increase in albuminuria after the acute stage has passed.

These experiments were undertaken to show the effect of variations in the amount of protein in the diet, using a strictly accurate method of estimation of the protein in the urine. Naturally, patients in an acute attack were not used, since they often show a very great increase in their blood urea, and a rich protein diet might be harmful.

Method.

20 c.c. of urine were used, acidified with 50 per cent. acetic acid, and the protein coagulated in the boiling-water bath for ten minutes. It was then washed with boiling water into a weighed filter-paper, and the washing continued until the filtrate was chloride free. It was then washed with boiling absolute alcohol, finally with ether, and dried to constant weight. A single urine takes from 15 to 30 minutes to filter and wash.

The amount of acetic acid employed is of importance both as regards ease of filtration and obtaining a protein-free filtrate. A preliminary experiment should be done on the urine of each fresh patient, and the optimum amount of acetic acid necessary found out, after which the same amount is used throughout for the urine of this particular patient. The urine, if not already acid when received, should be made just acid to litmus. 20 c.c. are measured into each of 5 beakers, and 2, 3, 4, 5, and 6 drops of 50 per cent. acetic added to each. They are then boiled for 10 minutes and filtered, and the minimum amount of acid needed to produce

a protein-free filtrate (tested with salicyl-sulphonic acid) determined. The amount of acid needed usually varies from 3 to 6 drops. The following experiments show the importance of the correct amount of acid:

Tube	1	2	3	4	5	6	7	8	
Added amount of 50 per cent. acetic acid in drops	4	6	8	10	12	14	16	18	20 c.c. of urine in each tube

Tube 1 filtered rapidly, 2, 3, and 4 gradually slower, and then the speed of filtration increased until 8 was as rapid as 1. On testing the filtrates with salicyl-sulphonic acid, tube 1 gave no precipitate. A gradually increasing precipitate was obtained along the series of tubes after 1, until the filtrate from 8 contained a very large precipitate.

The following experiments show the importance of the correct amount of acid in producing easy filtration, apart from obtaining a protein-free filtrate.

Five tubes used, each with 20 c.c. of urine.

Tube	1	2	3	4	5
Added amount of 50 per cent. acetic acid in drops	2	4	6	8	10

Complete filtration took five minutes in tube 3, by which time a quarter was still unfiltered in tube 1, tubes 2, 4, and 5 having a rather smaller quantity left. Tube 2 gave a faint precipitate with salicyl-sulphonic acid, the others no precipitate.

For estimations of urinary urea the hypobromite method was used; for blood urea, Maclean's modification of Van Slyke's method (6).

For plasma protein, the blood was collected into potassium oxalate, and the corpuscles centrifugalized out. 3 c.c. of plasma were taken and measured into 20 c.c. of 10 per cent. sodium sulphate. Five drops of 50 per cent. acetic acid were added, the protein coagulated by heating in the boiling-water bath for ten minutes and treated as mentioned above. Using sodium sulphate quite rapid filtration was obtained.

First Group of Cases.

Case I. Chronic case. Male, aged 27, ex-soldier. No history of trench fever, influenza, or other illnesses in the army. Had measles as a child; no previous illnesses, except syphilis in January, 1919, for which he was treated with N. A. B. until March, 1919. Since then he has had three consecutive negative Wassermann's. On August 1 he noticed a sudden swelling of the legs, puffiness of face, and headache. On admission, the heart was not enlarged and the arteries not thickened. Blood-pressure 120 mm. Hg. The urine was loaded with albumin, and granular casts were present.

Examination of kidney function.

Urinary urea 3·4 per cent. Diastatic value 20 +.
Blood urea 30 mg. per 100 c.c.

When examination started the diet was bread and butter, fish, vegetables, tea, and cocoa. No oedema was present.

Throughout the experiments he felt quite well and had no headache. No oedema was present.

No. of Experiment.	Amount of Urine in c.c.	Protein %.	Total Protein in Grm.	Diet.	Remarks.
1	1824	0·250	4·560	As above	
2	1397	0·254	3·547	„	
3	2308	0·181	4·000	„	
4	1966	0·280	5·506	„	
5	1140	0·471	5·375	Lean meat, cheese 4 oz., 4 eggs, peas and milk 2 pints	
6	1615	0·200	3·229	„ „	
7	2508	0·186	4·665	„ „	
8	2052	0·308	6·310	„ „	
9	2223	0·197	4·379	Tea and toast only	
10	1197	0·402	4·812	Rich protein diet, as above	

Case II. Acute case. Male, aged 9. No previous illnesses, except measles, when 2 years old. 7/10/19. Sudden onset of swelling of face and vomiting. Admitted 20/10/19. Urine contained much albumin and blood, no casts seen.

Examination of kidney function.

24 hours' specimen. Urea = 1·8 per cent. Diastatic value 10.
15 grm. of urea given.
Urea passed 1st hour 100 c.c.
2nd „ 100 c.c. Urea 2·6 per cent.

27/10/19. Urine showed very faint trace of protein with salicyl-sulphonic acid.

No. of Experiment.	Protein.	Diet.
1	Nil	Milk, bread and butter, milk pudding
2	Very faint trace	„ „ „ „ and fish
3	„ „	„ „ „ „ plus meat
4	Nil	As above, with 2 eggs and cheese
5	Nil	As above
6	Very faint trace	As above
7	Nil	As above

Case III. Chronic case. Female, aged 16. First admitted 18/5/18 with intense oedema, and urine solid with albumin. Later she developed ascites and was tapped many times. She was then put on a full protein diet, and improved somewhat, but extra feeding produced vomiting, so at Dr. Maclean's suggestion she was given 15 grm. of urea twice daily. After this, the oedema and ascites rapidly subsided, and she was discharged. Now (April, 1920) she is in very fair health and on ordinary diet at home, but is continuing her urea. She has no oedema, though the urine contains as much protein as before. If she stops taking the urea, the oedema at once returns.

Blood urea usually about 20 mg. per 100 c.c. After taking urea it never rose above 36 mg. Diastatic value 10.

No. of Experiment.	Amount of Urine in c.c.	Protein %.	Total Protein in Grm.	Diet.	Remarks.
1	2394	0·811	19·448	Full hospital	15 grm. of urea twice daily throughout
2	2272	0·798	18·131	„ „	
3	1482	0·817	12·108	„ „	
4	1539	0·688	10·588	„ „	
5	2480	0·735	18·228	„ „	
6	1539	0·610	9·4	Tea and toast only	
7	1225	0·811	11·091	Full diet	
8	1539	0·880	13·66	„ „	
9	2394	0·642	15·37	Tea and toast only	

Case V. Acute case. Male, aged 27. No previous illnesses. December, 1919, he had slight cold and sore throat. No headache, but slight puffiness of face was noted. Admitted 18/12/19. No oedema was present; heart not enlarged; arteries normal. Blood-pressure 130 mm. Hg. Urine contained a thick cloud of albumin and epithelial casts.

Examination of kidney function.

Urea concentration in 24 hours' specimen 1·2 per cent. Diastatic value 15.
15 grm. of urea given. Urine 1st hour 164 cc.
2nd „ 136 „ Urea 1·5 per cent.
3rd „ 132 „ „ 2 „ „
Blood urea 38 mg. per 100 c.c.

No. of Experiment.	Amount of Urine in c.c.	Protein %.	Total Protein in Grm.	Diet.	Remarks.
1	940	0·086	0·808	Fish diet	
2	314	0·189	0·593	„ „	
3	1568	0·122	1·913	„ „	
4	1539	0·042	0·646	„ „	
5	2223	0·014	0·311	Fish, cheese, milk 2 pints	
6	1568	0·032	0·502	„ „ „ „	
7	1368	0·040	0·547	„ „ plus 2 eggs	
8	969	0·030	0·291	„ „ „ „	
9	1710	0·008	0·137	„ „ „ „	
10	1140	0·034	0·388	Tea and toast only	No oedema, no headache. Felt well throughout
11	1801	0·037	0·666	„ „ „ „	

Case XIII. Subacute case. Female, aged 26. No previous illnesses, until November, 1919, when she had a miscarriage. Shortly after, swelling of face and legs was noticed and haematuria. On admission, February, 1920, slight oedema of ankles was present. Heart not enlarged, arteries not thickened. Blood-pressure 110 mm. Hg.

25/2/20. Urea concentration in urine 0·6 per cent. Diastatic value 2. Epithelial casts present.
Blood urea 182 mg. per 100 c.c.
16/3/20. Blood urea 37 mg. per 100 c.c.

No. of Experiment.	Protein %.	Diet.	Remarks.
1	0·042	Mainly carbohydrate — as little protein as possible	Date 17/3/20—or oedema present
2	0·067	„ „ „	
3	0·044	„ „ „	
4	0·044	„ „ „	
5	0·080	„ „ „	
6	0·076	„ „ „	
7	0·040	Meat, cheese 4 oz., 2 eggs, and milk ad lib.	
8	0·018	„ „ „	
9	0·036	„ „ „	Felt well throughout. No oedema, no headache
10	0·007	„ „ „	

Case VIII. Acute case. Female, aged 24. Admitted on account of sudden intense oedema and albuminuria. $7\frac{1}{2}$ months with pregnancy.

Examination of kidney function.

Urea 1·1 per cent. Diastatic value 10. Numerous hyaline casts.
Blood urea 28 mg. per 100 c.c.

No. of Experiment.	Protein %.	Diet.	Remarks.
1	0·436	Fish	
2	0·667	„	
3	0·936	„	
4	1·002	„	
5	0·588	„	
6	0·608	„	
7	0·655	Fish and chicken	
8	0·540	„ „ „	
9	0·778	„ „ „	
10	0·620	„ „ „	
11	0·667	„ „ „	Commencement of labour
12	0·077	„ „ „	Finish of labour—living child
13	very faint trace	„ „ „ plus 2 eggs, milk ad lib.	
14	0·038	„ „ „	
15	very faint trace	„ „ „	
16	very faint trace	„ „ „	

It will be seen that none of these cases had any cardiovascular changes, and show no evidence of inability to concentrate urea, except Case XIII, in whom there was considerable urea retention in the acute stage of the disease. This, however, soon disappeared. In many cases, especially with female patients, it was impossible to get accurate measurements of the urine passed in twenty-four hours, so that percentages only had to be used. When no special precautions were taken to obtain a constant amount of urine, the daily volume of urine passed varied considerably, and with it, the percentage amount of protein. Generally speaking, the larger the amount of urine passed, the smaller the percentage of protein it contained. There appears to be no evidence that increasing the protein intake within normal limits of diet produces any increase in the amount of protein passed in the urine. Case VIII is of interest, because in view of the very considerable albuminuria the indication was to induce labour; however, since functional tests of the kidneys showed no impairment, it was decided on these grounds to postpone this. The sudden drop in the protein excretion after labour is remarkable.

The importance of knowing the ability of the kidneys to deal with urea is shown well in Case III, where, in spite of the intense oedema, there was no evidence of urea retention. This case is in marked contrast to Case X (described later). Presumably, as the result of chronic changes, she will show later a gradually increasing difficulty in concentrating urea.

Second Group of Cases.

These cases all have the same factor in common, i. e. an inability to concentrate urea. All, with the exception of Case X, had raised blood-pressure and no oedema, and thus are in complete contrast to the previous group of cases, in which the kidney function, as shown by the urea test, appeared to be normal. Case X showed great inability to concentrate urea, and latterly a very high blood urea value, but, unlike the rest of the group, extreme oedema. Probably she was mainly an acute progressive parenchymatous case, as shown by the inability to excrete

chlorides, which was very marked. The urea retention present, together with the chloride retention, is typical of an acute condition, and should be compared with Case III already noted, in whom there was no tendency to urea retention, though the oedema was extreme for a long period.

Case IV. Chronic case. Male, aged 43, ex-soldier. Had nephritis in the army in October, 1918. This was his first attack—no previous illness of importance. He noticed slight swelling of face and ankles, which soon cleared up. Beginning of 1919 he noticed some frequency of micturition and failure of vision, with headache. In October, 1919, he had several transitory attacks of loss of consciousness, and was admitted because of this the same month. On admission, the heart impulse was half an inch external to nipple line. Retinitis was present. The arteries were thickened and the blood-pressure 238 mm. Hg. No oedema was present at any time while in hospital.

Examination of kidney function.

3/10/15. 24 hours' specimen. Urea concentration 1 per cent. Diastatic value 5. A cloud of albumin and a few epithelial casts were present.

		Urea.
15 grm. of urea were given :	1st hour urine 130 c.c.	—
	2nd „ „ 170 „	1 per cent.
	3rd „ „ 140 „	1·1 „ „

Blood urea 72 mg. per 100 c.c.

No. of Experiment.	Amount of Urine in c.c.	Protein %.	Total Protein in Grm.	Diet.	Remarks.
1	1311	0·20	2·622	Fish and chicken	
2	1995	0·142	2·833	„ „ „	
3	1710	0·168	2·873	„ „ „	
4	1283	0·325	4·370	Eating practically nothing, but a little milk and soda	Vomiting and slight fit
5	1710	0·175	2·993	Tea and toast only	
6	855	0·400	3·42	Fat bacon, potatoes, butter, tea and cream, i.e. protein free as possible	Feeling pretty well
7	1197	0·295	3·531	Almost protein free	Blood urea 39·5 mg.
8	1710	0·198	3·378	„ „ „	
9	1710	0·193	3·292	„ „ „	Feels well
10	1853	0·172	3·187	„ „ „	
11	1881	0·149	2·803	„ „ „	
12	1710	0·346	5·917	„ „ „	Severe headache started
13	1140	0·313	3·568	„ „ „	Still severe headache
14	428	0·516	2·208	Eating very little, as above	Intense headache. Very ill. Twitching of hands. Bled. Blood urea 38 mg. per 100 c.c.
15	855	0·320	2·736	„ „ „ „	
16	1710	0·160	2·736	Fish, chicken, cheese and milk	Feeling better
17	1425	0·180	2·594	„ „ „	
18	1995	0·120	2·394	„ „ „	Feels better, but condition steadily deteriorating
19	1710	0·169	3·042	„ „ „	No headache. B. P. 210
20	1995	0·123	2·454	„ „ „	
21	2565	0·112	2·873	„ „ „	
22	1853	0·287	5·318	„ „ „	Some headache. B.P. 230
23	1710	0·230	3·233	Tea and toast only	
24	1425	0·247	3·520	„ „ „ „	
25	1283	0·230	2·951	Fish, chicken, cheese and milk	B. P. 210

No. of Experiment.	Amount of Urine in c.c.	Protein %.	Total Protein in Grm.	Diet.	Remarks.
26	1853	0·232	2·299	Fish, chicken, cheese and milk	
27	1995	0·239	4·768	,, ,, ,,	
28	1539	0·222	3·417	,, ,, ,,	
29	1083	0·336	3·639	,, ,, ,,	Headache and vomiting
30	1425	0·490	6·983	,, ,, ,,	Severe headache, feels very ill
31	1283	0·554	7·108	,, ,, ,,	Severe headache, blood urea 92 mg. per 100 c.c.
32	855	0·568	4·856	,, ,, ,,	
33	1425	0·584	8·317	Tea and toast only	Headaches continuous, condition very bad
34	1140	0·570	6·498	,, ,, ,, ,,	
35	470	0·434	2·04	,, ,, ,, ,,	Much worse, very severe headaches, is having morphia

This patient died shortly afterwards. Post-mortem: there was no oedema. The heart weighed 17½ ounces, the left ventricle being greatly hypertrophied. The kidneys were rather small, the cortex not markedly contracted. The capsule was adherent. Sections of the kidney showed the glomeruli engorged and considerably fibrosed, with much thickening of Bowman's capsule. The cells of the convoluted tubules were swollen, and the lumen filled with granular debris; many were greatly dilated. The straight tubules showed the same changes, but to a lesser degree. There was a great increase in fibrous tissue throughout the kidney; great engorgement and universal round-celled infiltration. All vessels were much thickened.

Case X. Subacute case. Female, aged 25. One pregnancy two years ago, uneventful. In November, 1919, when four months pregnant, she noticed she

No. of Experiment.	Protein %.	Diet.	Remarks.
1	2·427	Fish	Feels fairly well, oedema increasing
2	2·328	,,	Blood urea 94 mg. per 100 c.c. Plasma protein 5·06 %. Urinary chlorides 0·01 %. Multiple puncture of legs performed
3	1·76	Milk	Draining freely from punctures
4	1·456	,,	Stopped draining
5	1·988	,,	Less oedematous
6	1·756	,,	Plasma protein 8·2 %, blood urea 52 mg. per 100 c.c. Urinary chlorides 0·23 %. Is much better
7	2·06	Fat and carbohydrate diet, salt free	
8	1·84	,, ,, ,,	Slightly more oedematous
9	2·068	,, ,, ,,	Much more oedematous; drain, with Southey's tubes. Urinary chlorides 0·076 %.
10	2·8	,, ,, ,,	Still draining; intensely oedematous and much worse
12	2·5	,, ,, ,,	Blood urea 198 mg. per 100 c.c. Plasma protein 4·57 %.
13	2·18	,, ,, ,,	Tremendous oedema. Moribund

was passing very little urine. Her face and legs became very oedematous. She was admitted to hospital and labour was induced forthwith. The urine

was nearly solid with albumin; B. P. 128. The heart was not enlarged. She was admitted to St. Thomas's Hospital in February, 1920, and did not feel particularly ill, oedema of legs being her chief complaint.

Examination of kidney function.

24 hours' specimen, + + +. Blood present and numerous epithelial and hyaline casts. Urea 1 per cent. Diastatic value 20.

15 grm. urea given. 2nd hour urine 110 c.c. Urea 1·2 per cent.

Died next day. P.M.: oedema of whole body; also much fluid in plural and abdominal cavities. Heart not enlarged. Kidneys slightly larger than normal; soft, pale, and watery. Capsule stripped very readily. Microscopically: glomeruli not much affected; cell outline indistinct and very slight fibrosis of tufts. Convoluted tubules showed extreme degree of destruction of epithelium; in many places no cell structure; in almost every case, lumen filled with granular or hyaline material. Many tubules enormously dilated. Straight tubules' cell outline very hazy, though a little less so than convoluted ones. Almost every lumen filled with hyaline material, or in some cases cellular casts. There was a moderate increase of fibrous tissue throughout, and an extreme degree of round-celled infiltration throughout. The vessels showed a slight fibrosis of media. Fat was present in sections stained with Scharlach R., chiefly at the bases of the cells of the convoluted tubules.

Case XI. Chronic case. Male, aged 6, admitted because of pain and swelling behind right ear. An immediate incision was performed. Soon after, the urine was noticed to be smoky and he was transferred to a medical ward. It was then found that six months previously he had been ill with slight swelling of face and feet. No oedema on admission, or later. Urine contained much albumin, blood, and granular casts.

Examination of kidney function.

24 hours' specimen. Urea concentration 1 per cent. Diastatic value 4.

15 grm. of urea given. Urea 2nd hour 1·4 „ „

3rd „ 1·7 „ „

No. of Experiment.	Protein %.	Diet.	Remarks.
1	0·353	Fish	
2	0·244	„	
3	0·446	„	
4	0·364	„	
5	0·250	„	
6	0·248	Milk, 1 pint per day	A little bronchitis present. Child has slight fever and cough. Appetite bad
7	0·310	„ „ „	
8	0·368	„ „ „	
9	0·307	„ „ „	
10	0·340	Practically full diet	Better, no cough. Eating well
11	0·357	„ „ „	
12	0·430	„ „ „	
13	0·325	„ „ „	
14	0·301	„ „ „	

It is interesting to note that the urea test, as noted above, was done when the patient was admitted and on a milk diet. Two months later, and some time after these observations were made, but for the albuminuria which persisted in large amounts, he appeared very well; was cheerful and always playing with other children. The urea test was repeated with the following results. He was now on full diet and no oedema was present.

Urea concentration in 24 hours' specimen 1·6 per cent.

		Urine passed.	Urea.
15 grm. urea given:	1st hour	130 c.c.	—
	2nd „	100 „	1·8 per cent.
	3rd „	85 „	1·7 „ „

So that, although the level of the urea is raised, there is still just as much, or more, inability to concentrate it.

Case XII. Chronic case. Female, aged 29. History of headache in November, 1918, and shortly after, slight oedema of face and ankles. This soon subsided and she went back to work. She noticed later that after standing all day there would be slight swelling of the ankles. She was admitted March, 1920, and then slight enlargement of the thyroid and some prominence of the eyes were noticed. On admission, the cardiac impulse was in the nipple line, blood-pressure 180, the arteries not thickened. She felt fairly well, did not complain of headache, and no oedema was present.

Examination of kidney function.

Urine −, albumin +, granular and hyalogranular casts present. Urea concentration 1·2 per cent. Diastatic value 2.

		Urine passed.	Urea.
15 grm. urea given:	1st hour	85 c.c.	—
	2nd „	83 „	1·4 per cent.
	3rd „	76 „	1·3 „ „

Blood urea 77 mg. per 100 c.c. Plasma protein 6·65 „ „

No. of Experiment.	Protein %.	Diet.	Remarks.
1	0·387	Fish	No oedema. Feels fairly well, is very pale
2	0·355	„	
3	0·378	Carbohydrate fat, salt free, as little protein as possible	Menstruating. Next observation five days later. Blood urea 50 mg. per 100 c.c.
4	0·462	Full diet, cheese and 2 eggs	No headache
5	0·311	„ „ „	
6	0·329	„ „ „	Plasma protein 5·9 %; blood urea 61 mg. per 100 c.c.
7	0·219	„ „ „	
8	0·337	Starvation, except tea to drink	
9	0·336	Starvation, except for tea	No headache, no oedema

After a further consecutive fourteen days on an almost entirely carbohydrate diet, the following results were obtained:

Urea concentration 0·7 per cent. in 24 hours' specimen.

		Urine passed.	Urea.
15 grm. urea given:	1st hour	90 c.c.	—
	2nd „	75 „	0·8 per cent.
	3rd „	90 „	0·95 „ „

Plasma protein 6·18 per cent. Blood urea 51 mg. per 100 c.c.

There was still no oedema, though the blood-pressure by now had risen to 200 mm. Hg. Thus it will be seen that the blood urea is only slightly raised as a result of carbohydrate diet; yet the urea test brings out the serious deficiency of the kidney.

In the second group of cases, all showed evidence of impaired kidney function and of inability to concentrate urea, as shown by Maclean's urea test, though both in Cases IV and XII the blood urea was at a normal, or almost normal figure, as a result of the low protein diet. It will be noted that Case IV always showed an increase of albumin in the urine when any uraemic manifestations set in, and also that on one occasion (see Experiment 14 on Case IV), as a result of diet, the blood urea was only 38 mg. per 100 c.c., and yet he had a severe attack of headache and uraemic symptoms, which seems to show that an increase in blood urea is not very serious in itself, but rather an indication of other changes.

Case X appeared to be a steadily increasing parenchymatous lesion. At one time it looked as if she was going to improve, until a sudden exacerbation was noted. Renal cases, at any rate where there is any suspicion of acute change, appear to need warm surroundings, and violent vasomotor disturbances are probably harmful. It will be seen that in Case XII the plasma protein was low throughout, although no oedema was present. So that a low figure cannot be the cause of oedema.

All cases were in bed throughout. In both groups of cases within the limits of the diet used, there is no evidence that variations in the amount of protein in the food caused any increase in the protein in the urine. In many instances the sudden change from a low protein diet to a rich one caused a diuresis, and this lowered the protein excreted. Case XII, a fortnight after the above experiments were finished, and having been on a very low protein diet the whole time, was passing as much protein as ever, as will be seen in the experiments noted below, in which the protein was estimated in specimens passed at 5 a.m., i. e. directly on waking, and at some later period of the day.

I. *Case IV (above)*. Slept rather badly, and preferred to be well propped up by day. He remained quiet, hardly moving.

No. of Experiment.	Time Specimen passed.	Protein %.
1	5 a.m.	0·234
	10 a.m.	0·211
2	5 a.m.	0·220
	10 a.m.	0·232

II. Female, aged 7. Had nephritis December, 1919, and continuous albuminuria since. Slept well, but by day was usually playing about in bed.

No. of Experiment.	Time Specimen passed.	Protein %.
1	6 a.m.	0·151
	12 noon	0·114
2	6 a.m.	0·058
	12 noon	0·105
3	6 a.m.	0·108
	12 noon	0·188
4	6 a.m.	0·237
	12 noon	0·146
5	6 a.m.	0·158
	12 noon	0·059

III. *Case XII* (*above*). Slept well; by day was sitting up in bed, sewing.

No. of Experiment.	Time Specimen passed.	Protein %.	Remarks.
1	5 a.m.	0·264	
	Midday	0·624	
2	5 a.m.	0·244	
	Midday	0·528	
3	5 a.m.	0·396	
	Midday	0·493	
4	5 a.m.	0·369	
	Midday	0·656	
5	5 a.m.	0·321	
	6 p.m.	0·666	After having been up 1 hour
6	5 a.m.	0·288	
	6 p.m.	0·657	" " " "
7	5 a.m.	0·387	
	6 p.m.	0·825	" " " "
8	5 a.m.	0·282	
	6 p.m.	0·630	" " " "
9	5 a.m.	0·226	
	Midday	0·418	Resting in bed doing no work
10	5 a.m.	0·294	
	Midday	0·360	" " " "

The blood-pressure was taken at various times, but no alteration found as a result of being up. The pulse-rate was usually about 10 beats a minute faster when up. It appears, from these experiments, that there is a definite increase in the amount of protein excreted by day, as compared with the amount excreted during the sleeping period. These results are presumably due to pressure changes.

IV. *Case XI* (*above*). Sleeps well by night; by days sits up in bed and plays about with toys.

No. of Experiment.	Time Specimen passed.	Protein %.
1	5 a.m.	0·912
	11 a.m.	0·895
2	5 a.m.	0·538
	11 a.m.	0·600
3	5 a.m.	0·381
	11 a.m.	0·674
4	5 a.m.	0·566
	11 a.m.	0·731
5	5 a.m.	0·610
	11 a.m.	0·906

The following two cases are included because of their interest. When first admitted, renal disease was considered as a possible cause of their symptoms. However, tests of the renal function showed no evidence of impairment, and thus they appeared to be cases of pure high blood-pressure, Clifford Allbutt's hyperpiesia. Clifford Allbutt includes among his cases those generally of middle age who only show a trace of protein and hyaline casts in their urine. Without investigation of the kidney function, it would be difficult to exclude renal disease in such cases. These two cases also appear to show the delicacy of Maclean's urea test.

Case XIV. Male, aged 54. Suddenly became unconscious, and was admitted for this reason. He had once fainted two years ago, and had been having some slight headache, otherwise complained of nothing. Heart impulse in nipple line; blood-pressure 200 mm. Hg. Arteries tortuous, but not especially thickened.

24 hours' specimen: protein, a definite cloud present. One or two granular casts were seen. Urea 1·7 per cent. Diastatic value 20.

		Urine passed.	Urea.
15 grm. of urea given:	1st hour	60 c.c.	3·5 per cent.
	2nd ,,	53 ,,	4·2 ,, ,,

Blood urea 40 mg. per 100 c.c.

Case XV. Male, aged 52. Has been a coal-porter all his adult life. No previous illnesses. Admitted because of a transitory right-sided weakness, with slight dizziness and headache. Heart ½ in. external to nipple line; blood-pressure 220 mm. Hg. Arteries tortuous, though not especially thick to the finger.

Urine, 24 hours' specimen: 1 granular cast seen and fairly numerous hyaline casts. Protein, a trace. Urea concentration 1·6 per cent. Diastatic value 10.

		Urine passed.	Urea.
15 gram. of urea given:	1st hour	190 c.c.	—
	2nd ,,	130 ,,	2·2 per cent.
	3rd ,,	95 ,,	2·8 ,, ,,

Blood urea, 40 mg. per 100 c.c.

Estimations of albumin by Esbach's method are, as is well known, only approximate. The following comparisons were made to see if the error was a constant one:

Estimation by Esbach.	Gravimetric Estimation.	Remarks.
0·425	0·313	The urine being diluted a half when necessary, and kept at room temperature 24 hours before reading
0·3	0·287	
0·4	0·247	
0·3	0·232	
0·5	0·568	
0·14	0·151	
0·7	0·584	
1·18	1·002	

The following results show the influence of temperature on Esbach readings: The precipitate was allowed to settle twenty-four hours in every case, the temperature being altered as follows:

	Estimation by Esbach.		Gravimetric Estimation.
1.	(*a*) 1·18	room temperature	1·002
	(*b*) 1·16	kept in ice safe	
2.	(*a*) 0·9	kept in ice safe	0·588
	(*b*) 0·6	room temperature	
	(*c*) 0·2	at 37° C.	
3.	(*a*) 0·93	in ice safe	0·655
	(*b*) 0·73	room temperature	
	(*c*) 0·2	at 37° C.	

It will be seen that the variations are considerable, and that the temperature has a marked effect on the readings. Possibly the method could be made more accurate if the graduations on the Esbach tube were adjusted to correspond with the readings given when kept over ice. Diluting the urine with various concentrations of salts, instead of water, made no difference to the readings.

Conclusions. It appears that variations in the amount of protein in the diet have no effect on the amount of protein excreted in the urine. In fact, such

increases in the diet do not increase albuminuria; if only percentage figures are taken, they may decrease it, owing to the diuresis produced by a rich protein diet.

The amount of protein in the urine examined at different times of the day shows wide variations. It appears to be lower in the urine secreted during sleep.

It is shown that the blood urea varies very considerably with the diet, and that an estimation of the blood urea is of much less value in appraising the impairment of kidney function than Maclean's new urea test. Further, the blood urea may be within normal limit, and yet all the manifestations of uremia be present.

The plasma protein may be below normal in cases with no oedema, and thus cannot always be a cause of oedema, as is often stated.

In conclusion, I must express my great indebtedness to Dr. H. Maclean for constant advice and suggestions throughout the progress of this work.

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THE ESTIMATION OF SUGAR TOLERANCE

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Of late years it has been increasingly recognized that the testing of carbohydrate tolerance by the study of the urine after the oral administration of glucose is essentially unsatisfactory. In this method of testing three factors are involved—the rate of absorption of the sugar, the action of the glycogenic and glycogenetic powers of the organism upon the absorbed sugar, and, finally, the excretion of sugar by the kidney. In attempting to estimate the capacity of the individual to deal with absorbed sugar—the object of any such test—the results are therefore liable to be vitiated by variations in the rate of absorption, and by changes in the excretory organs which lead to excessive or diminished excretion. Endeavours have been made to overcome any fallacies due to the rate of absorption by the carefully regulated intravenous administration of glucose. Woodyatt, Sansum, and Wilder (1) introduced glucose at a constant rate into a peripheral vein, and found that the normal individual could utilize 0·8 to 0·9 grm. per kilo per hour, without glycosuria being produced. For laevulose and galactose the tolerance was much lower, and for lactose practically nil. They found a lowered tolerance in exophthalmic goitre (0·65 grm.), and a slightly raised tolerance in acromegaly. Such methods, although they are capable of yielding exact statistical information and of application to man, are not likely to come into general clinical use owing to the elaborate nature of the apparatus required. Moreover, the introduction of the sugar into a peripheral vein is objectionable, since in studying tolerance we are interested in the fate of sugar absorbed from the intestine, via the portal system, and subjected to the action of the liver.

From the evidence available, differences in the rate of absorption of sugar given by the mouth are not likely to be an important source of fallacies in testing carbohydrate tolerance. Janney and Isaacson (2) state that the rate of absorption of pure glucose solutions in the normal individual is very constant, and the curves of hyperglycaemia, following oral administration of sugar, show a very fair uniformity in the work of various authors. The oral method of administration may therefore be regarded as sufficiently exact for clinical purposes.

A far more serious source of error, if the carbohydrate tolerance is estimated by the appearance of glycosuria, lies in the variations of the kidney threshold

for sugar. It may be pointed out that the kidney is normally excreting sugar, even when the blood-sugar is within normal limits—0·08 to 0·11 per cent.—and that at such levels the percentage of sugar in the urine corresponds fairly closely with that in the blood. When, however, a certain threshold of blood-sugar is reached, which in normal individuals may be placed at about 0·17 per cent., active secretion (the glycuresis of Benedict) occurs, and a glycosuria which is recognized by ordinary clinical methods of examination appears. Such glycosuria, in the older methods of testing carbohydrate tolerance, was accepted as evidence that the limits of tolerance had been reached. Its appearance depends, in reality, on the sugar threshold, and this is a variable factor. Thus, in cases of renal diabetes the threshold is abnormally low, and active glycuresis may occur at a very low level of blood-sugar. In one such case which we have had under observation, a pregnant woman excreted a urine containing 3 per cent. of sugar with a blood-sugar as low as 0·07 per cent., the condition clearing up on delivery. In another case, a mild diabetic, the threshold was also considerably lowered and sugar was excreted in abundance with a blood-sugar percentage of 0·13. In such cases of abnormally lowered renal thresholds, the amount of sugar in the urine is conditioned by the sensitiveness of the kidney rather than by the actual powers of the organism for dealing with sugar, and glycosuria cannot be regarded either as a criterion of the patient's tolerance or as a guide to treatment.

In other cases again, especially in severe diabetes and advanced nephritis, the glycuresis threshold may be considerably raised, and no marked glycosuria may occur until the blood-sugar has attained 0·25 per cent., or even more. In such cases an entirely false impression is given by study of the urine. Though in normal individuals the threshold is in the neighbourhood of 0·17 per cent. of blood-sugar, we are not justified in assuming that in any case to be tested the threshold is necessarily at this level; without an accurate knowledge of the height of the threshold with which we are dealing, we cannot regard the appearance of a clinical glycosuria as definite evidence that the blood-sugar has risen to abnormal heights. The appearance of glycosuria in a renal diabetes, after a small dose of sugar, is no evidence of a lowered carbohydrate tolerance, but merely an expression of the lowered renal threshold for sugar. Conversely, an increase in tolerance cannot be assumed in cases in which glycosuria is difficult to provoke, unless it can also be shown that the renal threshold is at a normal level.

The difficulties of estimating the individual's capacity for dealing with carbohydrates are therefore considerable, if we rely only on the appearance or absence of glycosuria as an indication of the presence or absence of an excessive hyperglycaemia, and cannot be overcome unless at the same time we estimate the sugar content of the blood.

With the development of methods for estimating blood-sugar, such as those of Bang or MacLean, it is possible, without repeated venous bleedings, to follow at frequent intervals the hyperglycaemia which results from the ingestion of

carbohydrates, and to deduce from the shape of the curve obtained how far the organism is dealing efficiently with its carbohydrate intake. By following the hyperglycaemia rather than the glycosuria, we eliminate fallacies due to the renal threshold, and, apart from variations in absorption which do not appear to be of much significance, obtain a fair picture of the glycogenic function of the organism.

Jacobsen (3), using Bang's method of blood-sugar estimation, was one of the first workers in this field. He was able to show that after ingestion of 100 grm. of glucose an appreciable rise in the blood-sugar occurred within five minutes, that the maximum level was usually attained in about thirty minutes, and that a return to normal occurred in most cases in about an hour and three-quarters. Similar results were obtained with cane sugar and starch. Fat in considerable amounts given with glucose exercised an inhibitory effect on the blood-sugar rise, owing, in his opinion, to interference with absorption. He tested five diabetics with 50 grm. of bread, and showed that in them the hyperglycaemia was more persistent than in the normal. The actual rise in the diabetic cases was not great, but the fall was prolonged. He points out the importance of frequent estimations, and attributes the conflicting and inconsistent results of earlier workers, many of whom estimated the blood-sugar at hourly intervals, to lack of this precaution.

Hopkins (4), also using Bang's method, tested his cases with 100 grm. of sugar in 420 c.c. of water given before breakfast. He states that a maximum hyperglycaemia occurs in $\frac{1}{2}$ to 2 hours in normals and in diabetics in $1\frac{1}{2}$ to 3 hours. He found markedly abnormal values in the hyperglycaemia of nephritics, the blood-sugar being still raised at the end of the third hour.

Janney and Isaacson, using Epstein's modification of the Lewis Benedict method, fasted their patients for 15 hours before the test, and gave 1·75 grm. of sugar for each kilo of body weight with 2·5 c.c. of water for each gramme of glucose. The blood-sugar was estimated before, and at hourly intervals after, the sugar was taken. If hyperglycaemia was still present two hours after the ingestion of the sugar, they regarded the carbohydrate tolerance as lowered. They found the test valuable in cases showing occasional glycosuria on a full diet, and in renal diabetes.

Hamman and Hirschmann (5) gave 100 grm. glucose dissolved in 300 c.c. of water, and gave 200 c.c. of water 30 and 60 minutes afterwards. They found active glycuresis with a blood-sugar approximating 0·17 per cent., as did also C. V. Bailey (6). The latter comments on the disproportion between the height of the hyperglycaemia attained and the amount of sugar given, and suggests that this is probably due to variations in intestinal absorption. He found a lowered renal threshold in early diabetics, and a raised threshold in severe cases. In 'renal diabetes' the blood-sugar curve ran a normal course. In nephritis the alimentary hyperglycaemia was high and prolonged. From the dates given by some of the above authors, it is obvious that if the appearance of glycosuria is to be taken as evidence of a hyperglycaemia, it is

advisable to collect the urine at frequent intervals during the test. In cases whose tolerance for carbohydrates is only slightly lowered, the period during which the blood-sugar is raised above the renal threshold may be brief, and if the samples are collected at long intervals the appearance of glycosuria may be missed, owing to dilution.

There seems to be a general agreement that in diabetics the alimentary hyperglycaemia runs an abnormally prolonged course, as compared with the normal individual, and that a diminution in carbohydrate tolerance can be detected in doubtful cases by following the blood-sugar. Though, according to many authors, nephritics also show a prolonged and excessive hyperglycaemia after administration of sugar, this is not likely to lead to confusion, since in nephritis the sugar threshold is raised, and consequently the case is unlikely to come under observation as suspected diabetes.

Method of estimating Sugar in testing Sugar Tolerance.

We have throughout used MacLean's (7) method for estimating blood-sugar. The method is simple and reliable, and requires only a very small amount of blood, so that samples can be taken as often as required. As we understand that the volume of the *Biochemical Journal* in which the method was first described is no longer available, we give a short *résumé* of the method here in the hope that it may prove useful to various workers who have written to us asking for details.

Method for estimating Sugar in 0·2 *c.c. Blood.*

The blood is obtained directly from a finger or from the ear. A special pipette[1] is used to collect and measure the blood. If the finger is used, a piece of rubber tubing is wound round the upper part to cause congestion towards the point, and a prick made with a needle on the back of the finger immediately above the root of the nail. The point of the pipette is placed in contact with the side of the drop, when the blood immediately flows in. If too much blood is obtained, the necessary adjustment is made by tapping the point of the pipette against the finger-nail, when some blood will escape. If sufficient blood is not obtained from the first prick, the rubber tube may be removed and the operation repeated as often as three times without fear of coagulation taking place. All possibility of coagulation may be prevented by dusting a little very finely ground potassium oxalate over the area from which the blood is to be withdrawn. If the prick is made about the centre of this area, the exuding blood comes into contact with the oxalate and coagulation is effectively prevented. Potassium oxalate, however, is not necessary, and we never employ it now, but its use might possibly prove of some advantage to a beginner. If the hand is cold it should be placed in hot water for a short time before taking the blood.

[1] Made by Hawksley and Sons, 357 Oxford Street, London.

The pipette must be kept scrupulously clean, otherwise the blood may not flow in. After each experiment it should be placed in a test-tube containing a mixture of hot sulphuric acid and potassium bichromate and left to stand there for some time. It is then washed with distilled water, followed by alcohol and ether, and thoroughly dried. When these precautions are taken there is never any difficulty in getting the blood.

Solutions required.

No. 1. A 15 per cent. solution of sodium sulphate to which acetic acid is added in the proportion of 0·1 c.c. to each 100 c.c. solution immediately before use.

No. 2. Dialysed iron solution. ('Dialysed iron, B. D. H.')

No. 3. Solution for estimating sugar in filtrate.

Potassium bicarbonate	12 grm.
Potassium carbonate (anhyd.)	8 „
Copper sulphate crystals	0·35 „
Potassium iodate	0·05 „
Potassium iodide	0·50 „
Distilled water to	100 c.c.

In making up this solution 12 grm. of potassium carbonate are dissolved by gentle heating (temperature not to exceed 37° C.) in 60 to 70 c.c. distilled water. The potassium carbonate is then added. The copper sulphate is dissolved in a separate beaker in a few c.c. of water and added to the mixture of carbonates without waiting for the carbonate to dissolve completely. After the resulting effervescence has passed over the complete solution of any remaining carbonate is brought about by heat. The iodate and iodide are now added, the solution thoroughly shaken, and filtered through a starch-free paper (No. 1 Whatman). The solution keeps indefinitely, but should be allowed to stand for a day or two before using it.

This solution must be standardized as regards its iodine content by taking 2 c.c. in 10 c.c. acid sodium sulphate solution and adding 2 c.c. of 75 per cent. hydrochloric acid. One minute after effervescence is completed, and after the mixture has been thoroughly shaken, it is titrated with N/400 sodium thiosulphate solution in the manner described later on when dealing with blood.

2 c.c. of this copper alkaline solution should require about 11 c.c. N/400 thiosulphate.

No. 4. An N/400 sodium thiosulphate solution made by adding 5 c.c. N/10 thiosulphate to some distilled water in a flask and making up to 200 c.c.

No. 5. A solution of 'soluble starch' about 1 per cent. strength.

No. 6. 75 per cent. hydrochloric acid solution. (75 c.c. concentrated HCl B. P., made up to 100 c.c.)

Details of Estimation.

From a burette 23·8 c.c. of acid sodium sulphate are introduced into a conical Erlenmeyer flask of heat-resisting glass. To this the 0·2 c.c. blood is added, and the pipette thoroughly washed out by alternately sucking in and

blowing out the solution. The mixture is heated until it just begins to boil, the flask being fitted with a rubber stopper through which passes a glass tube gradually tapering to a capillary point inside the flask. This allows the escape of air, and practically prevents loss of liquid. The flask is then cooled under the tap, and exactly 1 c.c. of dialysed iron added with constant shaking of the flask contents. After filtration through a No. 1 9-cm. Whatman filter-paper 20 c.c. of the filtrate are taken for the estimation of the sugar. To obtain this amount, filtration must be allowed to go on until all the liquid has passed through, as only about 21·5 c.c. can be obtained altogether. In diabetes cases 10 c.c. of the filtrate are taken and made up to 20 c.c. with acid sodium sulphate solution.

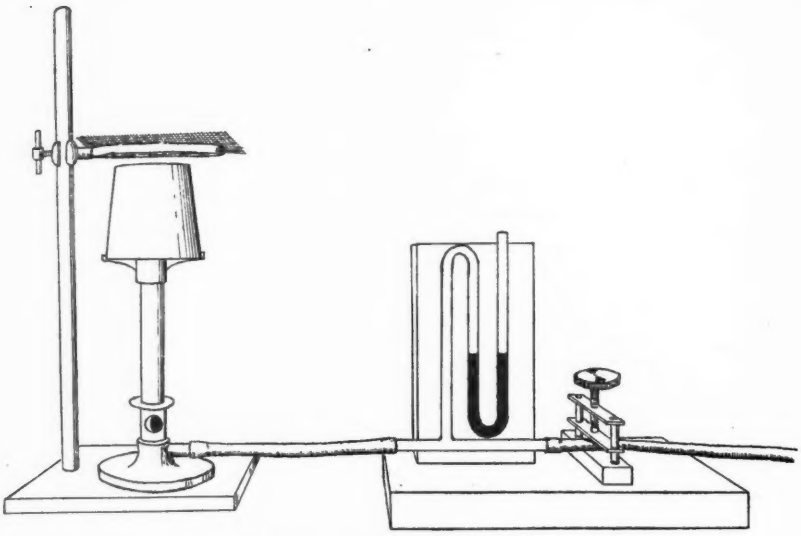

FIG. 1. Arrangement for regulating gas-pressure.

To this filtrate are added 2 c.c. (very carefully measured) of the alkaline copper solution and the mixture heated over a flame that brings the solution to brisk boiling in about 1 minute 40 seconds. To maintain a steady gas flame, it is useful to have a special manometer as shown in Fig. 1. The gas pressure is regulated by a screw clip, and the correct strength of flame required can be obtained by a few preliminary experiments, so that it is only necessary to mark the height of the fluid in the manometer to reproduce this pressure at any time.

Boiling is carried on for exactly six minutes, counting from the point at which the liquid begins to boil vigorously all over. The contents of the flask are then thoroughly cooled under the tap or by placing the flask in a large volume of cold water and 2 c.c. of 75 per cent. HCl added. The palm of the hand is placed over the mouth of the flask, and gentle agitation used, until the effervescence passes over, when the flask should be shaken with a circular motion at intervals for about a minute. N/400 sodium thiosulphate is now added from

a burette until the yellowish colour of the iodine has almost disappeared. At this point 2 to 3 drops of soluble starch are added and the titration completed, the end point being indicated by disappearance of the blue colour. The end point is quite distinct and never gives any trouble. The number of c.c. of thiosulphate used is then subtracted from the number used by 2 c.c. of copper solution alone, and the percentage of the sugar in the blood calculated from the table. Thus, if the reading obtained on titration was 8·98 c.c. thiosulphate, and if 2 c.c. of copper solution alone gives 11·05 c.c., the difference (2·07 c.c.) would represent the sugar present. From the table it is seen that 2·07 thiosulphate = 0·18 mg. sugar; therefore $\frac{4}{5}$ (the aliquot part of filtrate taken) of 0·2 c.c. blood contains 0·18 mg. sugar. 1 c.c. of blood will therefore contain

$$\frac{1}{1} \times \frac{5}{4} \times \frac{5}{1} \times \frac{0{\cdot}18}{1} \text{ mg. glucose} = 1{\cdot}12 \text{ mg.} = 0{\cdot}112 \text{ per. cent.}$$

TABLE.

(For estimation of sugar in 0·2 c.c. blood.)

Showing equivalent of glucose to N/400 thiosulphate solution.

N/400 thiosulphate.	Glucose.	N/400 thiosulphate.	Glucose.
c.c.	c.c.	c.c.	c.c.
0·12	0·03	2·61	0·22
0·25	0·04	2·74	0·23
0·38	0·05	2·86	0·24
0·50	0·06	2·99	0·25
0·62	0·07	3·11	0·26
0·73	0·08	3·24	0·27
0·86	0·09	3·36	0·28
0·99	0·10	3·49	0·29
1·13	0·11	3·61	0·30
1·26	0·12	3·74	0·31
1·39	0·13	3·87	0·32
1·53	0·14	3·99	0·33
1·67	0·15	4·12	0·34
1·80	0·16	4·24	0·35
1·94	0·17	4·37	0·36
2·07	0·18	4·49	0·37
2·22	0·19	4·62	0·38
2·35	0·20	4·74	0·39
2·49	0·21	4·87	0·40

In testing patients for carbohydrate tolerance, some authors have insisted on a preliminary period of starvation. The necessity for this is by no means obvious. Sufficient time should, of course, elapse to allow the blood-sugar to return to a normal level after the immediately preceding meal, and for this 3 to 4 hours will suffice. Provided this precaution is taken, the form of the curve does not appear to be influenced by previous carbohydrate intake. This is well seen in Chart 1, which shows the variations in the blood-sugar of a normal individual during 7½ hours. Two mixed meals were taken at the points indicated. The curve of the second meal closely resembles that of the first. It will be seen that the urinary excretion of sugar was roughly parallel to that of the blood-sugar, though at a somewhat lower level. The chart also indicates how impossible it is to define a 'normal' blood-sugar level. The concentration of the

blood-sugar in the normal is varying from hour to hour with the carbohydrate ingestion, and what is a normal blood-sugar 30 minutes after a carbohydrate meal is definitely abnormal four hours later. To enable us to state whether a blood-sugar is normal or not, we must know the nature of the preceding meal,

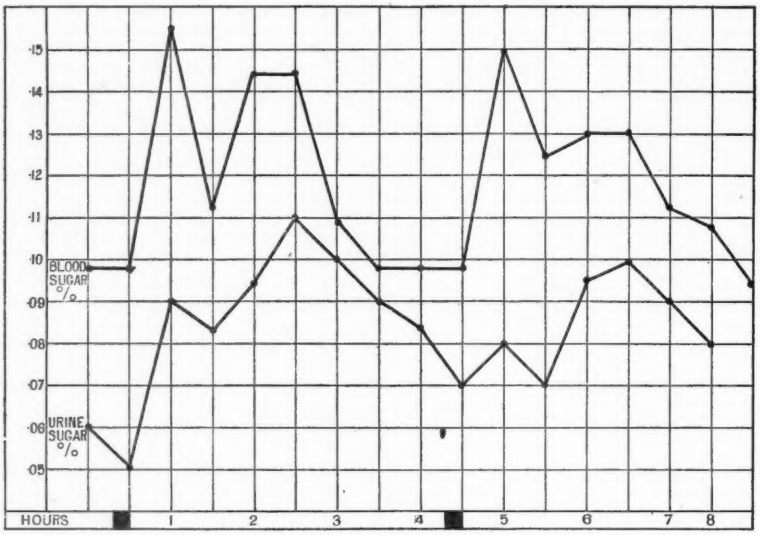

CHART 1.

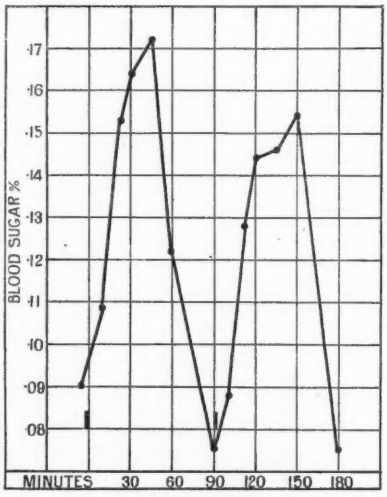

CHART 2.

and the interval after ingestion at which the blood sample was taken. An isolated observation on the blood-sugar gives us but little information, since, even in many cases of ordinary diabetes, the blood-sugar can be reduced under certain conditions to as low a value as 0·08 per cent. by starvation.

Chart 2 is given to illustrate the effect of a preceding dose of glucose. Fifty grm. of glucose were given at the beginning of the curve, and, one and a half hours later, when the first rise in blood-sugar had terminated, a second similar dose was taken. Though the second rise is slightly less marked than the first, the actual time during which hyperglycaemia persists is almost exactly the same in both instances. It does not seem necessary therefore to fast the patient for more than three or four hours before testing. As far as the amount of ingested sugar is concerned we have in doubtful cases used 50 grm. of glucose, which, as will be explained later, elicits an adequate response, but in studying the reaction of definite diabetics we have often used a considerably smaller dose. The sugar was dissolved in 150 c.c. of water, but the amount of fluid given appears to exercise little, if any, influence on the shape of the curve.

A sample of blood should be taken immediately before the dose of sugar is given to determine the original level of blood-sugar. After this, samples should be analysed every half-hour for two hours. Since only 0·2 c.c. of blood is required for an estimation—an amount easily obtained from a single finger-prick—the discomfort to the patient is minimal.

In the diabetic we have in some instances reduced the blood-sugar by one or two days' starvation to within normal limits, but, as will be seen in a later chart, the response to a given dose of glucose appears to run approximately the same course irrespective of the height of the blood-sugar at the commencement of the test.

The Response in the Normal Individual.

In Chart 3 the curves following the ingestion of varying amounts of glucose (5 to 100 grm.) are given. The curves are all taken from the same individual, and show that after a certain dose is reached—about 25 grm.—further increase in the amount of sugar given does not increase the actual height of the resulting hyperglycaemia. The increase in the dose tends rather to prolong the period during which the blood-sugar is raised, than to increase the actual height of the curve. In Chart 4 the results of successive 50-grm. doses of glucose are seen. In curve I one dose of 50 grm. was given; in curve II a further similar amount was given 15 minutes after the initial 50-grm. dose; in curve III 50 grm. were taken at 15 and 30 minutes after the original dose. It is obvious that the interpolation of a second and third dose, at a time when absorption is in full swing, fails to raise the height of the curve, though the time during which hyperglycaemia is present is considerably prolonged. It is of interest to note that the rise in the blood-sugar in the normal tends to be arrested in the neighbourhood of the threshold for glycuresis—about 0·17 per cent. The significance of this will be discussed later in connexion with the diabetic curve.

The delicacy of the test is very striking, as little as 5 grm. of glucose producing an appreciable rise. After a single dose the blood-sugar returns to normal within two hours, and a period of hypoglycaemia often follows. Jacobsen in his cases also noted the occurrence of subnormal levels at the end of the rise.

For the purpose of comparison, and for the sake of certain points of interest which they possess, we give a chart showing the effect on the blood-sugar of certain other sugars and starches (Chart 5). Laevulose appears to be the only sugar tested which gave no definite rise. This fact was confirmed in several

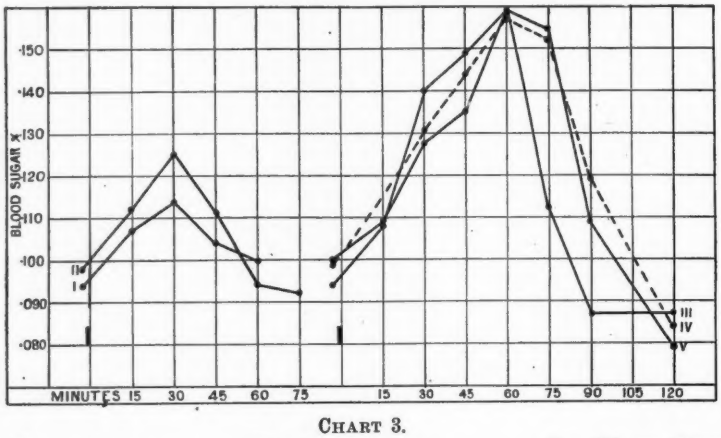

CHART 3.

I = 5 grm. glucose. III = 25 grm. glucose. V = 100 grm. glucose.
II = 10 ,, ,, IV = 50 ,, ,,

Effects on blood-sugar of varying doses of glucose.

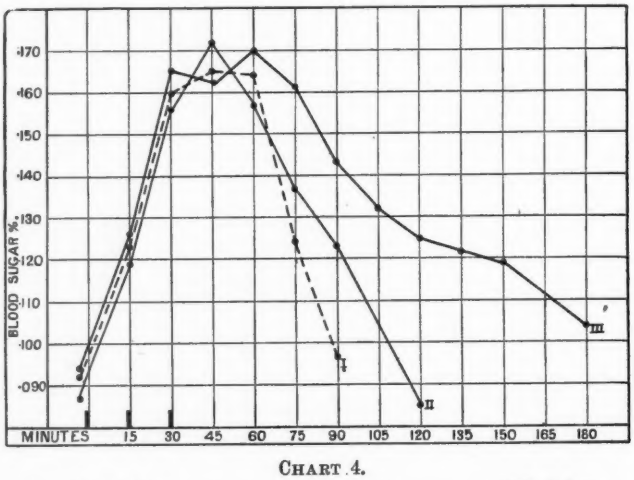

CHART 4.

I. A single dose. II. 2 doses. III. 3 doses.

Effects of successive 50-grm. doses of glucose at 15′ intervals.

individuals, and with different samples of laevulose. The rapid splitting and absorption of the starches and disaccharides is very noticeable, the curve obtained with cane sugar or potatoes showing quite as rapid a rise as that of glucose. Indeed, potatoes seem to be a very suitable material for testing the diabetic patient, since they are looked on by most diabetics with less suspicion than an

actual dose of sugar. Lactose shows a slow and rather prolonged rise, but is obviously easily absorbed by the adult. The curves obtained after the ingestion of galactose and maltose resemble that of glucose; the same phenomenon is seen as in the glucose curve—a rapid rise to the neighbourhood of 0·17 per cent., followed by a sharp fall. The hyperglycaemia, resulting from the ingestion of carbohydrates, appears in the normal individual to be limited to about this level—the threshold level for glycuresis—and cannot easily, if at all, be forced above it. In this fact lies the explanation of the work of Taylor and Hulton (8) on the difficulty of provoking glycosuria in the healthy individual.

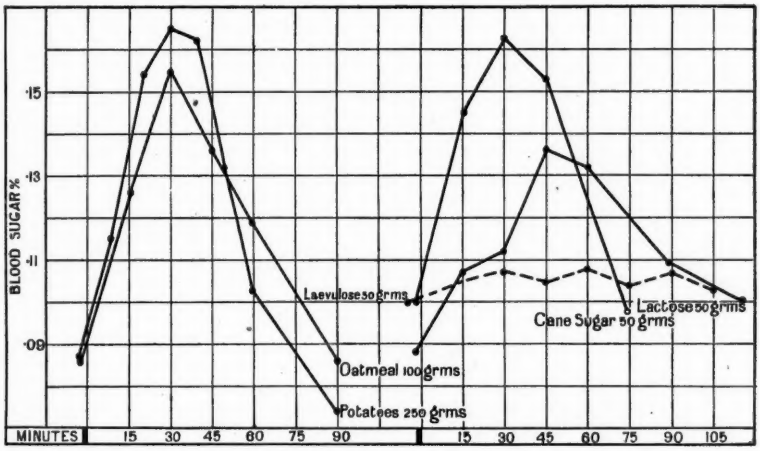

CHART 5. Effect of equivalent amounts of various carbohydrates.

The Diabetic Curve.

In Chart 6 the curve obtained from a severe case of diabetes, after the ingestion of 40 grm. of glucose, is contrasted with that of a normal after 50 grm. The blood-sugar in the diabetic had been reduced to nearly normal by appropriate treatment. At the end of the first hour, the rise in blood-sugar is the same in both cases—70 mg. per 100 c.c.—but from this point onwards there is no resemblance between the two curves. While in the normal the blood-sugar falls rapidly, and in the next thirty minutes has regained its original level, in the diabetic it continues to rise steadily, and attains its maximum figure in two and a half hours. Even at this point there is no tendency to any abrupt fall, but a slow decline, which at the end of four and a half hours still leaves the sugar content of the blood at 0·233 per cent., as contrasted with an original level of 0·130 per cent. A comparison of the two curves immediately suggests an explanation of the shape of the normal curve. It appears almost certain that the check in the rise of the normal's blood-sugar during the second thirty minutes is not due to any falling off of absorption, nor can the abrupt fall in the third thirty-minute period signify that absorption has come to an end. In the

diabetic the blood-sugar is still rising during this time, and absorption is therefore still going on, the amount of sugar taken being adequate to raise the sugar content of the blood by 130 mg. per 100 c.c. In contrast to this, the normal curve after reaching 0·16 per cent.—a total increase of 64 mg. per 100 c.c.—shows a rapidly diminishing rate of ascent, and then an abrupt drop. The fall in the normal curve cannot therefore be due to the cessation of absorption, and two alternatives only remain—that a great rise in catabolism of sugar suddenly occurs, or that the sugar is removed from the blood and stored more

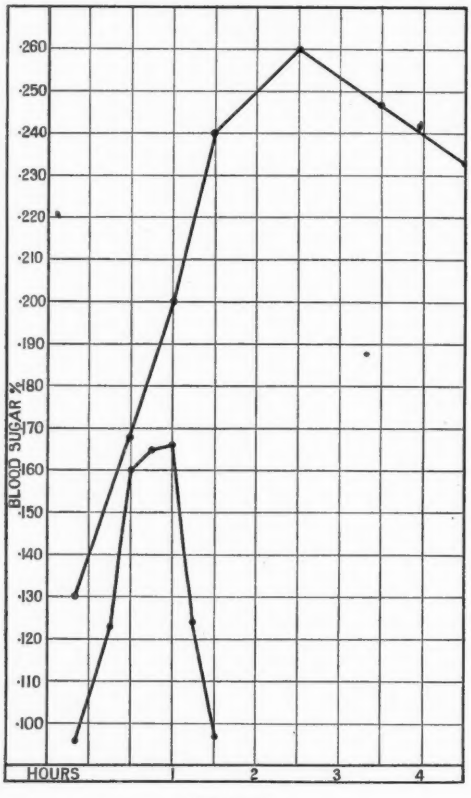

CHART 6.

quickly than it is absorbed. For the first of these alternatives there is no evidence, and such a procedure would evidently be highly wasteful. We must assume therefore that the drop in the normal curve is caused by the sudden intervention of a storage mechanism, which abstracts the sugar from the blood more quickly than it enters, and as a result masks the later stages of absorption. The absence or impairment of such a mechanism in diabetes makes the curve of alimentary hyperglycaemia in the diabetic a much truer picture of the absorption rate than in the normal, though, even in the diabetic, the result is complicated

by a considerable loss of sugar via the kidneys, and by any catabolism of sugar that may still be taking place. These two factors may largely account for the gradual decline that is seen at the end of the diabetic curve.

From the curves given above to show the effect of the absorption of glucose and other sugars on the blood-sugar content of the normal individual, it appears that the storage mechanism comes into action at about a threshold of 0·16 to 0·17 per cent. blood-sugar—a figure which corresponds closely to the renal threshold for glycuresis. Storage begins at about the level at which active excretion of sugar by the kidneys commences, and hence in the individual with unimpaired capacity for dealing with carbohydrate and a normal renal threshold no glycosuria follows the ingestion of even very large doses of carbohydrate. That the healthy mechanism is highly efficient is shown by the difficulty or impossibility of forcing the blood-sugar above this threshold. As has been shown above, additional large doses of glucose given during the height of absorption fail to raise the blood-sugar above this level, which may be regarded as the extreme upper limit of the range of blood-sugar content in the normal. It is due to the action of this mechanism that a disproportion exists between the amount of sugar given and the height of the resulting hyperglycaemia. This lack of proportion is not in reality evidence of variations in absorption, as suggested by C. V. Bailey, but of efficient storage. In the case of glucose 25 grm. suffice to raise the blood-sugar to its maximal level, while further increase in the amount given tends merely to prolong without raising the curve. With smaller doses, however, as shown in Chart 3, the rise is roughly proportional to the amount of sugar given.

That storage is still actively continuing, after the normal blood-sugar curve has regained its original level, is probable from a comparison of the curve of a severe diabetic. In the latter the rise continues long after the termination of the hyperglycaemia in the normal, indicating that absorption is still in progress. Possibly the hypoglycaemia, which is often seen at this stage, is an indication of the activity of the mechanism. The ingestion of a second dose of glucose at this stage produces however, as we saw above, a response which differs but little from that produced in the fasting individual.

In the diabetic this mechanism apparently fails in varying degrees, and the extent of its failure can be gauged by the curve of alimentary hyperglycaemia. As a working rule, if the blood-sugar fails to return to its original level within about 1½ hours, after a single 50-grm. dose of glucose, we may consider that a defect in storage is present. In our experience the healthy individual is able to deal with such an amount within this time.

It is probable that the main site of the storage is the liver. Though we have been able to demonstrate definite differences in the blood-sugar content of capillary and venous blood taken from the resting arm—the capillary blood-sugar being often considerably in excess of the venous—such differences bear no direct relationship to the height of the capillary blood-sugar. If the fall in the normal curve were largely due to such storage in the muscles a direct relationship

would be expected. As there is no evidence of this, it is probable that the storage capacity of the liver is the main factor involved, but direct evidence of this can only be obtained by animal experiments. Such experiments we are at present carrying out.

Before proceeding to the milder grades of defect in sugar metabolism, we give a few curves illustrating the effects of sugar ingestion in the more severe type of case, since such observations are always of clinical interest. Chart 7 illustrates the effect of 25 grm. of carbohydrate (potatoes) on a moderately severe case of diabetes. Before the upper curve was taken, the patient had been receiving a diet which was slightly in excess of his tolerance level for carbohydrates. The blood-sugar before the test was in consequence high. The lower curve was obtained after two days' starvation, which had reduced his blood-sugar to a low level. In both the initial level is not regained until five hours have elapsed, showing that a very definite defect was present. The preceding period of starvation had no effect on the length of the curve, and only minor differences are noticed between the curve starting from the initial low blood-sugar and the curve at the beginning of which the blood-sugar was high. For purposes of comparison a normal curve following the ingestion of 25 grm. carbohydrate (potatoes) is included. Chart 8 shows curves obtained from a severe case of diabetes with 25 grm. of glucose and with 250 grm. meat. The ingestion of protein is apparently without effect on the blood-sugar.

In well-marked cases of diabetes, such as the above, the results of the test, though of interest from a scientific point of view, are not important for purposes of diagnosis, though we would emphasize the necessity of estimation of the blood-sugar in excluding renal diabetes. In cases, however, in which occasional glycosuria is present, the significance of which remains in doubt, very valuable information may be obtained.

The method enables us to gain an insight into the patient's capacity for dealing with carbohydrate more certainly, and more rapidly, than a dietetic test, in which the appearance or absence of glycosuria is alone considered. As has been already pointed out such glycosuria is in itself no evidence of hyperglycaemia unless the renal threshold is known, and in some cases we can detect a definite delay in storage, even though the blood-sugar content does not rise above the renal threshold for glycuresis throughout the test. The sugar content of the blood is, in other words, better estimated directly, than indirectly through a study of the renal excretion. In Chart 9 we give the curve of blood-sugar following the ingestion of 25 grm. of glucose by a patient in whom glycosuria had been noticed at intervals for two years. No evidence of acidosis or other signs of diabetes were present. As contrasted with the normal curve given in the same chart, a definite defect in storage appears to be present. The fall is considerably slower, and the blood-sugar regains its original level an hour later than in health. Though the actual height of the curve does not exceed the normal, and though no glycosuria occurred throughout the test, the gradual and delayed fall suggests that a minor degree of deficiency was present, and a

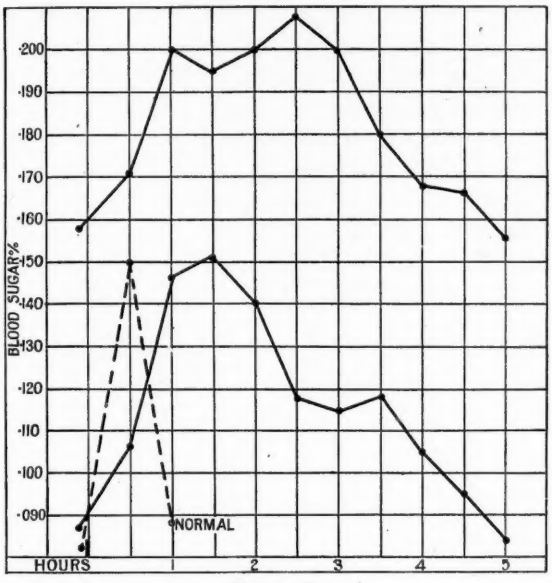

CHART 7.

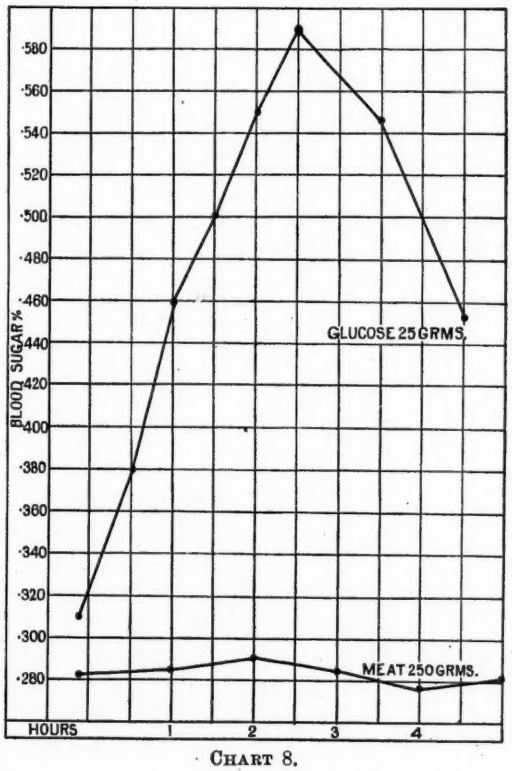

CHART 8.

limitation of the carbohydrate in the diet resulted in a considerable improvement in the general health of the patient.

In Chart 10 two curves obtained from suspected cases of diabetes are contrasted. Curve I gives the result of the ingestion of 50 grm. of glucose by a girl of 17, in whose urine a reducing substance was constantly present. Here the hyperglycaemia seemed to run an absolutely normal course, the fall of the

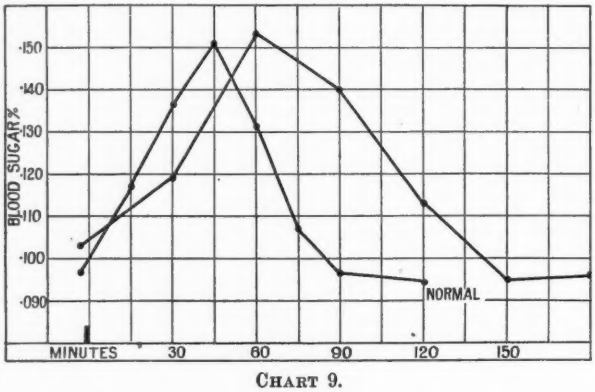

CHART 9.

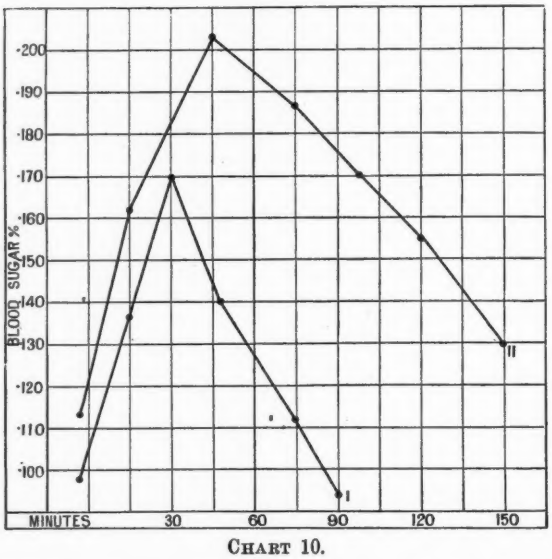

CHART 10.

curve is abrupt and rapid, and no suggestion of a failure in the storage mechanism is present. The reducing substance proved to consist mainly of a pentose with occasional slight traces of glucose. Though such a case requires to be watched, there does not appear to be any immediate indication for dietetic or other treatment.

In curve II a failure to deal adequately with the carbohydrate (50 grm.

glucose) ingested is undoubtedly present. Though the rise in the blood-sugar is not so marked as in some of the cases of definite diabetes given above it is undoubtedly excessive and provokes but a poor response from the storage mechanism. The fall is slow, gradual, and still incomplete at the end of two and a half hours. Glucose and traces of acetone were frequently present in the urine of this patient when on a full diet. There is no doubt that a grave defect was present. In such milder types of glycosuria the value of an examination of the blood-sugar curve following the ingestion of sugar is undoubted, and gives useful indications as to the necessity for treatment. The question as to whether, in the normal, ingested sugar is converted into some intermediate product before it can be utilized is as yet unsolved, but a study of the blood-sugar in diabetes suggests that in the diabetic the failure of some mechanism, by which in health sugar is abstracted from the blood and stored, is an important, if not the most important, defect. How far the whole phenomena of the disease are conditioned by the deficiency in this first stage in metabolism is as yet uncertain, but that hyperglycaemia and glycosuria are an inevitable result is certain. Of milder grades of defect in this mechanism, the first indications can be readily obtained by the estimation of the blood-sugar content at sufficiently frequent intervals after carbohydrate ingestion. The method has as yet been but little employed in this country, but it appears to us to open a fruitful field for work, and probably a valuable means of diagnosis in the early stages of the disease, during which some amelioration by treatment may be expected. For the diagnosis of the advanced case of diabetes it is unnecessary, though, even in such cases, fairly frequent estimations of blood-sugar are of great value both for treatment and prognosis. In detecting minor deviations from the normal, which may constitute the earliest warnings of the development of diabetes, the test appears to have a very definite use. Indeed, the estimation of the sugar tolerance by examination of the blood-sugar at varying intervals, after the ingestion of carbohydrate, is the only means by which a satisfactory graphic representation of the actual condition of the carbohydrate storing mechanism can be obtained.

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THE REACTION OF THE SPINAL FLUID DURING CEREBRO-SPINAL FEVER

By C. SHEARER and T. R. PARSONS
(Report to the Medical Research Committee)

The reaction of the cerebro-spinal fluid during health and disease has been recently the subject of considerable investigation, and widely different results have been obtained. In large part they are to be explained by the fact that most of the investigators in this subject have taken no precautions to prevent the escape of the carbon dioxide from their fluids, before or during examination. Most of the figures so far given for the reaction of this fluid are, therefore, for this reason, too much on the alkaline side. In another communication (Parsons and Shearer, 1920) (1), it has been shown that the spinal fluid in man is slightly more acid in reaction than the blood, and that at the normal tension of carbon dioxide in the body it may have a P_h as low as 7·2–7·3.

Recent work, on the whole, has shown that in non-meningitic disease the cerebro-spinal fluid undergoes little change in reaction from that of the normal condition; even in such diseases as tubercular meningitis, lateral sclerosis, and syphilis of the cord and brain, little or no change can be demonstrated in this respect.

In epidemic cerebro-spinal fever, however, as Levinson (1916 and 1917) (2) has shown, a very marked change in reaction usually takes place. In the titration of 1 c.c. of spinal fluid in 20 c.c. distilled water with N/100 H_2SO_4, using methyl red as an indicator, normal fluid required 2·0–2·4 c.c. of H_2SO_4 to give a neutral tint, while the fluid from a case of cerebro-spinal fever required only 0·7–1·3 c.c. acid. By the Sorensen colorimetric method he found normal fluid to have a P_h of 7·4–7·6, in cerebro-spinal fever it had usually a P_h of 7·3–7·4, and in some cases was even as low as 7·1. These determinations were made on fluid immediately after withdrawal from the body, and presumably before much of the carbon dioxide had escaped. He noted that the alkalinity of the fluid rapidly increased on standing in contact with air. Thus, in one sample, the P_h of which on withdrawal from the body was 7·4, at the end of twenty-four hours in contact with air its P_h had changed to 8·2. We have here an explanation of the high

figures given for the P_h of the cerebro-spinal fluid by many previous workers, such as Bisgaard (1914) (3), Weston (1916) (4), Hurwitz and Tranter (1916) (5), Felton, Hussey, and Bayne Jones (1917) (6), and other investigators.

Beyond the fact that he examined the fluid immediately on withdrawal from the body, Levinson (1917) (8) took no special precautions to prevent his fluid from coming in contact with air, for it was allowed to drop directly from the end of the lumbar puncture needle into the test-tube in which it was examined. We now know that in the case of blood collected in a similar manner a very considerable portion of its carbon dioxide is given off under such conditions. In the following estimations, for this reason, care was taken not to let the spinal fluid come in contact with air during collection and so to part with its carbon dioxide. It was a simple matter to attach a short length of thin rubber tubing to the end of the lumbar puncture needle, and by means of this run the spinal fluid into the bottom of a test-tube under a considerable quantity of paraffin oil. The indicator could then be added to the fluid by means of a long pipette passed down through the floating oil, so that it was never necessary to expose the fluid to the air at any time before or during examination. The fluid was received in the first place directly into a colorimetric test-tube, which was immediately placed in the comparator and the standard buffer solutions matched against it. These were prepared after the manner recommended by Clark and Lubs (1916) (7). Bromthymol blue and phenol red were used as indicators. It is worthy of note that all samples of spinal fluid examined in this way invariably gave a lower P_h value than samples of the same fluids examined after coming in contact with air in the manner adopted by Levinson (1917) (8).

In another paper it has been shown (Parsons and Shearer, 1920) (1) that with the spinal fluid we are dealing with a carbonic acid-bicarbonate system, in which the fundamental assumptions of Hasselbalch (1916) (9) hold, with reference to a solution in which the whole of the combined carbon dioxide of the solution is in the form of sodium bicarbonate, where the P_h of the fluid, the concentration of combined carbon dioxide (Bik), and the dissolved carbon dioxide (CO_2) are related by the formula:

$$P_h = pk_1 + \log. \left(\frac{Bik}{CO_2}\right)$$

where pk_1 is the magnitude involving the first dissociation constant of carbonic acid and the degree of ionization of the sodium bicarbonate in the solution. Our measurements would seem to show that the whole of the combined carbon dioxide in the cerebro-spinal fluid is in the form of sodium bicarbonate. In addition to this, there are probably present in the fluid small quantities of substances that increase its buffer efficiency above that of a sodium bicarbonate solution of the same alkali reserve.

In the following observations the alkali reserve of the spinal fluid was determined by the method recommended by McClendon (1918) (10), a N/10 HCl being used with bromcresol purple as an indicator. Three titrations were made on each fluid, the mean of the three being taken as the final reading.

The three following cases give the results of determinations on what may be considered normal fluids, using the above-described methods.

Case I. Normal fluid. Collected from a man aged 37 years, who was lumbar-punctured under suspicion of being a case of commencing cerebro-spinal fever. Fluid was clear and transparent, showing no cellular elements, and was sterile on subculture. A few hours after the lumbar puncture was made the patient made a complete recovery.

$P_h = 7{\cdot}4$, alkali reserve = 0·025 N.

Case II. Normal fluid. Case of early syphilis of the cord. Fluid clear and transparent, contained no cellular elements, and was sterile on subculture.

$P_h = 7{\cdot}4$, alkali reserve = 0·031 N.

Case III. Normal fluid. Tubercular meningitis in a female child aged 8 years. Fluid clear and transparent.

$P_h = 7{\cdot}3$, alkali reserve = 0·025 N.

Cerebro-spinal fever cases. Case I. Cerebro-spinal fever resulting in death. Fluid turbid, and showing the presence of the meningococcus.

$P_h = 6{\cdot}9$, alkali reserve = 0·012 N.

Case II. Cerebro-spinal fever case resulting in death after the second lumbar-puncture. Serum administered. Fluid very turbid, showing the presence of the meningococcus.

1st lumbar puncture, 10 c.c. serum administered.

$P_h = 7{\cdot}0$, alkali reserve = 0·013 N.

2nd lumbar puncture.

$P_h = 6{\cdot}9$, alkali reserve = 0·010 N.

Case III. Cerebro-spinal fever with recovery. Fluid turbid, the meningococcus present.

1st lumbar puncture. Serum administered.

$P_h = 6{\cdot}9$, alkali reserve = 0·011 N.

2nd lumbar puncture. Serum administered.

$P_h = 7{\cdot}1$, alkali reserve = 0·020 N.

3rd lumbar puncture. Serum administered.

$P_h = 7{\cdot}3$, alkali reserve = 0·020 N.

The second puncture was made twenty-four hours after the first, while the third was made three days after the second. In distinction to these cases in which all precautions had been taken to prevent the fluid from coming in contact with air after withdrawal from the body, it is interesting to compare with them a number of estimations on fluids collected in the ordinary way where these precautions had not been observed. These fluids had been collected in contact with air, the ends of the test-tubes in which they had been collected were then sealed in a blow-pipe flame, and the tubes dispatched through the post and examined about twenty-four to thirty-six hours after they had been taken from the body. Their alkali reserve was not determined.

Normal fluids.	*Cerebro-spinal fever fluids.*
Case *I.* $P_h = 8{\cdot}3$	Case *IV.* $P_h = 7{\cdot}8$
„ *II.* $P_h = 8{\cdot}4$	„ *V.* $P_h = 7{\cdot}4$
„ *III.* $P_h = 8{\cdot}5$	„ *VI.* $P_h = 7{\cdot}4$
	„ *VII.* $P_h = 7{\cdot}5$

In both the normal and the cerebro-spinal fever fluids of these cases the rise in the P_h due to the loss of the carbon dioxide is clearly shown, when these values are compared with those of the previous ones where the carbon dioxide was present. It will be noticed that, despite this, the cerebro-spinal fever fluids were more acid than the normal fluids.

Conclusions.

It has been shown that if rigorous precautions are taken to prevent the cerebro-spinal fluid on withdrawal from the body from coming in contact with air, its P_h, as determined colorimetrically, has a much higher acid value than when these precautions are not taken. Levinson's (1917) (8) discovery that in cerebro-spinal fever there is marked acidosis of the spinal fluid is confirmed. This acidosis, however, is much more marked than that found by Levinson, if the escape of all carbon dioxide from the fluid is avoided on collection. The present observations show that the P_h of the fluid in this disease may sink as low as 6·9 [1] with an alkali reserve of 0·010 N. This figure fixes the hydrogen-ion concentration of the fluid well on the acid side of the real point of neutrality.[2]

In consideration of the great sensitivity of the respiratory centre to slight changes in the P_h of the blood, it is of considerable interest to determine the effect of the administration of alkali with serum in cases where a marked acidosis is present. Levinson's demonstration that in this disease the alkali reserve and P_h of the spinal fluid rapidly improve under serum treatment when recovery takes place is also confirmed. In fatal cases, on the other hand, serum treatment would seem to have little influence on the P_h and alkali reserve.

This peculiar acidosis of the cerebro-spinal fluid in meningococcal infection, in contradistinction to what we find in other meningeal infections, is probably due to the ease with which this germ can attack the sugar present in the spinal fluid. The meningococcus can rapidly break down glucose, forming lactic acid, and this sugar is present in a variable quantity in the cerebro-spinal fluid.

In cerebro-spinal fever it has frequently been noted that there is often a striking difference between the clinical symptoms shown by a patient suffering from this disease and the degree of infection or number of meningococci found in the spinal fluid on lumbar puncture. It is possible that in such cases the degree of acidosis is the controlling feature. If the spinal fluid contains less than the normal amount of glucose or other substance from which the meningococcus may form acid, or the particular strain of the organism setting up infection does not possess the faculty of forming the usual amount of acid, then the patient's fluid will show but slight change in reaction from the normal condition, although large

[1] The buffer used for this determination was at the conclusion of the observations measured by the gas-chain method and its P_h value confirmed.

[2] It should be remembered that this value was determined in the laboratory at room temperature; at body temperature this fluid would be just on the alkaline side of the absolute point of neutrality.

numbers of the meningococci may be present. The absence of any marked acidosis of the spinal fluid in such cases would account for the mild clinical symptoms. It may prove that those types of the meningococcus responsible for fatal cases are always strong acid-forming strains.

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FATAL BRONCHIOLITIS AND BRONCHO-PNEUMONIA CAUSED BY *B. INFLUENZAE* OF PFEIFFER DURING AN INTER-PANDEMIC PERIOD

By ARCHIBALD MALLOCH[1] and LAWRENCE J. RHEA

Although we have recently passed through several waves of a pandemic of influenza, and although much work has been done, yet the specific cause of the disease has not been determined with certainty. Most of us who were not engaged in medical work during the pandemic of 1889–92, and who do not remember the controversy after the discovery of Pfeiffer's bacillus in 1892 (12), took for granted that this organism was definitely the cause of the disease. Our ideas were, however, rudely shaken by the very varied reports of the bacteriological findings in the cases of the pandemic of 1918–20, and at present there are four views as to the aetiology of influenza. (1) That it is due to a specially virulent strain of *B. influenzae* of Pfeiffer, although the serious effects of other micro-organisms, acting as 'secondary invaders', is granted. (2) That it is caused by a filterable virus. (3) That, like measles and other exanthemata, it is a general or systemic infection of unknown causation, and that various organisms, such as the pneumococcus, streptococcus, &c., acting as 'secondary invaders', step in and produce very severe and at times fatal effects upon the patient whose resistance has been lowered by the attack of influenza. (4) That influenza is due primarily to a mixed infection in the widest sense of the term; i.e. that *B. influenzae*, the pneumococcus, the streptococcus, and, perhaps, other agents, growing in the closest association and interacting upon one another, produce an 'obligate complex virus' (Sahli (13)).

'Influenza' is a much abused clinical term, and no diagnosis is made with so little thought by some medical men. Although the causative agent has not been finally determined it is not necessary to isolate it to make a diagnosis of influenza if there is a pandemic with numerous cases about us on every side and when the disease sweeps across whole continents as rapidly as man can travel. We must assume that between pandemics there are isolated or sporadic cases of influenza, and that at each onset of a widespread pandemic the disease does not arise *de novo*. How are we to diagnose these scattered cases? In the light of our present knowledge it is impossible to do this, as we do not know

[1] Beit Memorial Fellow.

[Q. J. M., Jan., 1921.]

the cause of the disease, and, as various investigators (Davis (4), Jehle (7), Mathers (10)) have shown, small or even large epidemics, simulating influenza in the closest way, may be caused by the pneumococcus, streptococcus, *Micrococcus catarrhalis*, and other organisms.

Moffitt, in 1908 (11), and others, did not hesitate to call their cases 'influenza' where *B. influenzae* of Pfeiffer was found, but we do not feel that we can be so dogmatic about our sporadic cases, which were seen in France in 1916 and 1917 at the 3rd Canadian General Hospital (McGill), when we take into consideration the opposing ideas concerning the aetiology of influenza. We think, however, that we are justified in publishing the clinical, bacteriological, and pathological aspects of this series to show what type of acute respiratory disease and what lesions may have as their cause *B. influenzae* of Pfeiffer. It might also be added that, through the experimental work lately carried out upon monkeys by Blake (2), Pfeiffer's bacillus would seem to have again become the favourite amongst the claimants to the title of 'the cause of influenza'.

Salient Clinical Features.[2]

The majority of the patients were between 30 and 40 years of age and one was 44. On the whole the physique of these men was not very good. Several of the patients had suffered from 'winter colds' and one had had pneumonia.

Onset. The illness came on insiduously in most of the cases, but rapidly in two of them. There was no history of a chill, few complained of any great amount of pain, and certainly this was not so marked a feature as in lobar pneumonia. Cough and expectoration were amongst the first symptoms noted, but none complained of coryza.

Diagnosis on admission to hospital. Three had been regarded as examples of 'P. U. O.', several had been diagnosed as 'bronchitis', and two were thought to have been suffering from pneumonia.

Physical examination. Taken as a whole, the nine patients showed little difference on physical examination, and the clinical course of the disease was very similar in these cases. From first to last the most outstanding features on inspection were great dyspnoea and cyanosis of varying degree. Often acute respiratory distress was written clearly on their faces, and any voluntary movement on the part of the patients made this only the more pronounced. Herpes was not seen in any of the cases. In all the cases fine râles could be made out on palpating the chest. Only if there was much consolidation, as in Case IV, was tactile fremitus increased. Areas of dullness were occasionally made out, but in many instances pulmonary resonance was increased.

If we exclude Case IV, where blowing breathing was heard over the whole of the right lung, and if we forget for the moment those instances in which there were small patches of bronchial breathing, and concentrate our attention on

[2] Fuller details are given in the summary of case reports.

the sounds heard over the lungs in all the cases, we shall be able to emphasize the most characteristic sign obtained on physical examination. The breath-sounds were heard everywhere, but they were accompanied by fine, peculiarly sharp, metallic râles, which seemed to be produced just beneath the bell of the stethoscope at the surface of the lung. These were present from the day of admission until the day of death. They were heard in greater numbers during inspiration, but also during expiration. Accompanying these fine sharp crepitations were other adventitious sounds: rhonchi and sibillant râles, which formed, so to speak, the background of the picture. In short, the signs were those of a very generalized bronchiolitis.

Pain. Few complained of much pain throughout their illness.

Delirium. Only two patients were delirious.

Sputum and its bacteriology. In the first two cases the sputum was not examined microscopically, but, from the results of the post-mortem examination of these cases, we learnt to associate certain macroscopic features of the sputum with the finding of *B. influenzae* of Pfeiffer under the microscope. In the remaining seven patients *B. influenzae* was found to be by far and away the predominating organism of the sputum. The most characteristic feature of the sputum was its nummularity, although this quality did not necessarily show itself at the outset. As a rule, during the last few days of life, the patients brought up the sputum with increasing difficulty. Sometimes the sputum was not entirely composed of muco-purulent masses, but the pellets lay in a clear menstruum of mucus. The expectoration was never 'rusty', but very small traces of blood in streaks on the surface of the masses were occasionally noted. Generally it had very little odour, but in one case there was a peculiar 'musty' smell about the bed and sputum cup from the tenth day until death on the fifteenth. The nummular masses, when they first appeared, were greyish white in colour, but later they became yellowish white. In Case IX the sputum was described on the last day of disease as being 'semi-nummular', and we wish to suggest (1) that this loss of definite nummularity may possibly have been due to the increase of organisms other than *B. influenzae*, and (2) that had the patient lived the sputum might have been no longer 'musty' but foetid.

We have been unable to find in the literature a quite satisfactory or definite account of either the gross or macroscopic characteristics of the sputum in such cases as we are describing. Therefore, as a typical example of what was observed, we shall take the expectoration of patient IX on admission to hospital (tenth day): 'In about three hours' time the patient expectorated 50 c.c. of sputum, which consisted of many moderate-sized, tenacious, yellowish-white muco-purulent masses. These were quite airless and lay in a small quantity of clear mucoid menstruum. The individual masses did not run together and were distinctly nummular. No blood stains were seen. The masses floated in water. Smears were made and stained with a weak solution of carbol-fuchsin by heating to the steaming point. An abundant bacteriological flora was found. By far the greatest number of organisms were very small ones, and, on first

examination, appeared to occur in pairs, i. e. as fine diplococci. On looking more carefully, however, it was seen that they were really very short bacilli with deeply-staining polar granules. The cytoplasm connecting the granules was stained only a very faint pink, but the lateral edges of this stood out as two clear-cut pink lines joining the granules of the organism. For the most part, these micro-organisms lay together in clumps of fifty or so, and throughout the smear were present in enormous numbers. There were a few diplococci, which had the appearance of *Micrococcus catarrhalis*, but, even in contrast with these, the polar-staining bacilli were very small. A very few definite slender bacilli were seen, but most of them possessed polar-staining granules. A film was also stained by Gram's method, and a very few organisms, morphologically like pneumococci, were seen as well as countless Gram-negative bacilli. These latter were smaller than the pneumococci and occurred for the most part in clumps. Sometimes in these clumps a few Gram-negative diplococci were seen, in form like the *Micrococcus catarrhalis*, but in other places the Gram-negative bacilli made up the whole clump. There were numerous polymorphonuclear leucocytes, but few contained the fine Gram-negative bacilli.'

Hübschmann (6) has written of the association of other organisms with *B. influenzae* in the sputum noted by us above.

He remarked upon the significance of finding *M. catarrhalis* together with Pfeiffer's bacillus and suggested that these organisms were in some way helpful to one another in thriving. Contrary to his results, however, although we saw *M. catarrhalis* in the sputum, we never found it in the exudate of the terminal bronchi.

Bacteriological cultures from the sputum. As a further description of the sputum of these cases we shall continue with that of patient IX: 'On the twelfth day of disease, after cleansing out the mouth with a normal saline solution and making the patient give a hard cough, a specimen of sputum was obtained in a sterile Petri dish and cultures made from this on blood agar. Many colonies of *B. influenzae* were grown. Smears from these showed many varieties of involution forms which are well illustrated in text-books of bacteriology.'

Circulatory system. In all cases the pulse-rate was much quickened, and the lowest rate recorded in any of the cases was 92, and the average all through was about 125 per minute. As the disease progressed the picture was that of a gradually failing heart. Sometimes visible and palpable pulsation in the epigastrium told the tale of a weakening right ventricle, as did the gradual loss of sharpness in the pulmonary second sound. Acute endocarditis due to Pfeiffer's bacillus was found at autopsy in two cases, but was not recognized before death.

Urine. A trace of albumin was found in several of the cases, but never any casts, so we are unable to confirm the idea that the kidneys are badly affected in these cases of infection with Pfeiffer's bacillus.

Temperature. The charts do not reveal any typical picture, but high fever

was present at some time or other during the course of all the cases. Fever was of the remitting type. It is important to note that even when the fever was less the pulse and respiratory rates were not appreciably decreased.

Leucocytes. The number of white blood cells was estimated in only two cases, neither of which showed any complication at autopsy, and were found to amount to 22,400 in one case and 21,000 per c.mm. in the other.

Complications. These were only in connexion with the circulatory system and were not diagnosed before death; they will be referred to below with the pathological findings, but we have already described them fully in a previous paper (see Bibliography 9). Briefly, there was purulent pericarditis in Case II, and endocarditis in Case IV (aortic) and in Case VII (mitral and aortic), all caused by *B. influenzae.*

Diagnosis. In all these cases, except I and II, a diagnosis was made before death of capillary bronchitis or broncho-pneumonia due to the *B. influenzae.* This was based upon the fever, marked dyspnoea, and cyanosis; upon the signs of a general capillary bronchitis (fine, sharp, metallic râles heard all over the chest); upon the gross character of the sputum, which was nummular at some time in the course of the disease, if not continuously so; and lastly—and this is the *sine qua non*—upon the finding of *B. influenzae* as the predominating micro-organism in the sputum. Acute miliary tuberculosis must be excluded, for the physical signs may be very similar in both diseases. Exclusive of many cases of pneumonia following the inhalation of poison gases, and of the cases of pneumonia which occurred in the first wave of the pandemic of influenza, we had under our care in the 'pneumonia hut' of a base hospital in France, from January 1, 1917 to August 1918, 172 cases of lobar pneumonia and 97 of broncho-pneumonia. It is worthy of note that amongst these we did not find any cases of diffuse capillary bronchitis due to any other organism than the *Bacillus influenzae.*

As seen in Case IV, there is sometimes great difficulty in differentiating the confluent type of broncho-pneumonia, caused by *B. influenzae* of Pfeiffer, from lobar pneumonia; and even *post mortem* the lung on inspection and casual palpation (*vide infra*) presented the appearance of that organ in the latter disease. The history of the onset of the illness must be carefully taken, and a microscopic examination of the sputum is necessary to exclude lobar pneumonia, as we shall show. Patient IV was admitted on the third day of illness, and on the sixth day a diagnosis of lobar pneumonia was made and the Infectious Disease Report filled out. The case was so diagnosed as there was dullness throughout the right lung, except along its anterior border close to the sternum, with blowing breathing and bronchophony everywhere. There were also signs of some consolidation at the base of the left lung. Some doubt, however, was felt about the diagnosis, as the exact date of the onset of the illness was obscure, and as rhonchi and sibilant râles, besides fine 'crackles', were heard over the consolidated right lung, and these findings have not been common in our cases of lobar pneumonia. As it turned out, the

diagnosis had to be changed on the twelfth day, as the sputum had become distinctly nummular and *B. influenzae* was the prevailing organism in it. The patient died on the thirteenth day and confluent broncho-pneumonia was found at the autopsy.

Duration of disease. The minimal duration was six days and the maximal twenty-one days. There were four deaths out of a total of nine between the tenth and twelfth days inclusive.

Treatment. This was purely symptomatic; all the patients were transferred to a special hut where it was possible to arrange for a plentiful supply of fresh air. A steam tent was tried in one case, but did not make the patient more easy. Venesection did not produce any material benefit. Stimulants, such as oil of camphor, strychnine, adrenalin, and pituitary extract, seemed to have little effect. Codein was given for the cough to prevent unnecessary exertion; and morphine combined with atropin was administered if the patient was very restless or sleepless.

Morbid Anatomy and Post-mortem Bacteriology.

Pleura. A very fine fibrinous pleurisy, difficult to detect except by reflected light, was a common finding. In one case there was a slight excess of clear fluid in one pleural sac, but infected fluid or frank pus were never found.

Lungs, trachea, and bronchi. In the majority of the cases the lungs were very voluminous. Dark purplish areas of atelectasis at the borders of the lower lobes were noted in several of the cases. These were about 1·5 cm. in diameter and stood out in sharp contrast with the pale surface of the emphysematous lungs elsewhere. On the surface of these areas were seen small yellowish dots of broncho-pneumonia.

Muco-purulent bronchitis was a constant finding; in several cases there was very marked congestion, and in two instances there were haemorrhages in the mucous membrane of the bronchi. In one of these latter cases the trachea also showed acute haemorrhagic inflammation, but tinges of blood were seen in the sputum on one day only. In the primary and secondary bronchi the exudate was yellowish or yellowish green in colour in practically all the cases, but as one opened up the smaller branches down to the terminal ones it changed in character and became of a greyish-white colour. This capillary bronchitis was the most constant feature of the lungs *post mortem*, and even in those cases where practically no consolidation could be felt, and in other cases in parts of the lungs which showed no consolidation, on gently pressing upon the organ, then wiping away blood and serous or odematous fluid from the cut surface and compressing the lung again as before, the position of the mouths of the bronchioles, before invisible, was now made evident as greyish-white muco-purulent matter showed itself as very fine drops. On one occasion it was noted that there were two kinds of exudate in the terminal bronchi: a drier one which could be pulled out of the bronchioles with the aid of dissecting forceps;

and another form which was much softer and could easily be picked up with a platinum-wire loop. It was from the contents of these extremely fine branches of the bronchial tree that we obtained material from which our final diagnosis of broncho-pneumonia due to *B. influenzae* of Pfeiffer was made.

Considerable care was exercised to avoid contamination of the material used in making cultures, and to prevent blood flowing down into the bronchi on removing the lungs from the body a ligature was tied around all the structures at the root of the lung, and the organ severed from the body by cutting between the ligature and the heart and mediastinum. The surface of the lung was cauterized—we found an old spoon very convenient for this procedure—and then with a sterile knife a cut was made through the burnt surface into the substance of the organ. The exudate from the bronchioles was picked up with a platinum wire and media inoculated, preferably human blood agar. Smears for immediate examination were at the same time prepared. On many occasions film preparations and cultures made from the larger bronchi were also examined. Smears from the terminal bronchi of all the nine cases showed organisms like Pfeiffer's bacillus in morphology and in staining reactions, and these micro-organisms only. Cultures were not made from the fine bronchi of Case V, but in all the others *B. influenzae* was grown in pure culture, except in Case IX, where, although this organism grew out, the plate was contaminated by air organisms. Polymorphs were always seen in the exudate, but, in contrast to the other cases, those seen in the exudate from the fine bronchi, and also from the larger ones of Case VIII, were packed with the organisms.

In Case VI the bacilli of Pfeiffer were found only in fine strings of mucus; some of these strings were so slender that their entire width came into the field of the oil-immersion lens. The strings of mucus varied in length, but several of them extended from one end of the smear to the other. *B. influenzae* was found in the smears from the larger bronchi as well, and, as was noted in Case V, they were often present in larger numbers than in the terminal bronchi. But whilst the microscopic flora of the fine bronchi consisted of *B. influenzae* only, that of the secondary and primary bronchi was made up of other organisms as well; namely, those like the pneumococcus, *Micrococcus catarrhalis*, streptococcus, &c., on different occasions. Thus, as was to be expected, this flora closely resembled that of the sputum. Cultures from the secondary bronchi in Case VI gave a growth of pneumococci and streptococci only; and in Case VIII a mixed growth of *B. influenzae* together with *Staphylococcus albus*. This change from the single organism in the terminal bronchi to the more varied flora in the larger ones has been noted before by various writers.

Whilst discussing the condition of the bronchioles, it is of some interest to note that in Case IX a dilated bronchiole, about the size of a pea, full of yellow pus, was present in a small atelectatic area of the left lower lobe. Smears and cultures from this showed *B. influenzae*. Boggs (3) in 1905 described six cases of bronchiectasis from Osler's service at the Johns Hopkins Hospital and the rôle played by *B. influenzae* in its formation. After this series of nine cases

was completed we had under our care a man 32 years of age, who died on the eighth day of disease. His sputum had a very musty odour, was nummular at first, but later became confluent. Smears showed very many bacilli of Pfeiffer, but mixed with very many other organisms. At the autopsy was found confluent broncho-pneumonia of the right lung and the same patches of atelectasis which we shall describe in Cases VIII and IX. In the left lung the disease was apparently of a later stage and there were many bronchiectatic cavities, none larger than a pea in size, lined with a pyogenic membrane. On opening up the cavities the fine lumen of the bronchiole could be seen in the wall. They were filled with fetid-smelling pus, and smears and cultures showed many *B. influenzae* mixed with air organisms. Recently one of us (A. M.) has seen here in England a somewhat similar case, but of longer duration, accompanied by nummular sputum containing large numbers of Pfeiffer's bacilli, and at the post-mortem examination extensive bronchiectasis in one lobe was found. We wish to suggest that the cases of so-called 'purulent bronchitis' seen in some of the front line areas, as well as in England, may have been due primarily to *B. influenzae*.

In Cases II and III, in which there was little consolidation of the lungs, the cut surface showed fine greyish-white dots varying in size from the lowest point of visibility up to 3 to 4 mm. in diameter. Some of these small areas had become confluent and were separated by very congested areas. The appearance was very like that of young tubercles. Microscopically there was acute purulent bronchiolitis, peribronchiolitis with the formation of minute abscesses where the alveolar walls close to the bronchioles had disappeared. Bacilli like Pfeiffer's bacillus in morphology and staining reactions were seen here. Broncho-pneumonia was present in the alveoli about the bronchioles which were filled with pus. The exudate in the air sacs contained little fibrin and fewer polymorphs than is the case in lobar pneumonia; on the other hand, many lining epithelium cells lay free in the alveoli. In some of the air sacs a clear-staining, hyaline-like material was found. The interalveolar septa were somewhat thickened and the alveoli varied very much in size, some being collapsed, and there were also areas of marked emphysema. These variations probably find their explanation in the inflammation of the bronchioles, some being almost completely blocked with exudate, and in some cases these plugs of muco-pus probably allowed no air to pass, and in others permitted it to do so in one direction only. Where the epithelium was denuded from the wall of the bronchiole beginning organization with young fibroblasts might in some places be observed. The blood-vessels were everywhere much congested, even in the pleura. Besides the acute lesions described above there was also a mild grade of an old peribronchial tuberculosis of the healing type. There can be no doubt that this latter lesion was not active. Sections were stained for tubercle bacilli, but none were found. In this case *B. influenzae* was obtained in pure culture from the terminal bronchi.

Although the capillary bronchitis described above has been the most

characteristic feature of the lungs *post mortem* there were often definite areas of consolidation, also noted before death. This was most marked in Case IV, where the whole of the right lung except the anterior border of the lobes was very firm, and to the eye could not be differentiated from true lobar pneumonia until the organ was sectioned across. Even on casual palpation the lung seemed to be solid, but by feeling carefully slight irregularities or a 'lumpiness' could be detected; and on cutting into the lung, and inspecting the cut surface closely, small areas of healthy tissue could be seen between those of confluent broncho-pneumonia. In this case, also, there were confluent masses in the left lower lobe.

Small areas of consolidation were found in both lungs of Cases V and VI, and larger masses in the right lower lobe of Case VII, and in both upper and lower lobes of the left lung of Case IX.

Pericardium and pericardial sac. In Cases VII and VIII an excess of clear fluid was found *post mortem*, and in Case VII there was also an excess of fat in the epicardium. There was a slight increase in the amount of pericardial fluid in the case of patient II, but it was turbid and contained a few yellowish flakes of fibrin. Smears showed *B. influenzae* of Pfeiffer and no other organisms.

Myocardium. In all the cases cloudy swelling of the heart muscle was noted at the autopsy, and in Case IV it was recorded that the myocardium was distinctly soft; acute and chronic endocarditis were also present. The muscle was fatty in the heart of Case VII, and, besides the acute and chronic endocarditis, there was dilatation and hypertrophy of the wall of the right ventricle and concentric hypertrophy of the myocardium of the left chamber.

Endocardium. In Case IV the inner surface of the arch of the aorta showed numerous puckered scars typical of syphilitic disease and the bases of the aortic cusps were sclerosed. On the free margins of these cusps were found several granular excrescences of acute infection, but there was little damage done to the cusps themselves. One vegetation measured about 7 mm. in diameter. The lining intima of the aorta was quite free from disease in Case VII, but there was sclerosis of a mild grade of the aortic cusps as evidenced by old scarified areas at the sites of the corpora Aurantii. On the free edges of these cusps were present acute granular vegetations of yellowish colour, the largest of which measured about 5 mm. in diameter. There was a small, rather flat, recent vegetation, reddish in colour, on the septal cusp of the mitral valve, but there was no gross evidence of any old change in this valve. In smears made from the cores of the vegetations in the former of these two cases, micro-organisms, like *B. influenzae* in staining reactions and in morphology, were found. No other organisms were seen. In the smears from the centre of the vegetations of the latter of the two cases no bacteria were seen. Pfeiffer's bacillus was grown in pure culture from the cores of the vegetations in both cases, the surface first being burnt to prevent contamination.

Blood cultures. These were done in practically all of the autopsies and proved sterile except in No. IV, where acute endocarditis was present. In this

case *B. influenzae* was obtained in pure growth. It may be remarked that the majority of the autopsies were done within twelve hours of death.

Aorta. Moderate sclerosis was present in Case II, and in Case IV the scarred and 'wash-leather' appearance characteristic of syphilitic disease was seen.

Other organs at autopsy. 'Cloudy swelling' of the spleen was present, but the organ was not enlarged except in Case VII (complicated by acute endocarditis); here it measured 18 by 12 cm. and was soft and diffluent. 'Cloudy swelling' was the only lesion noted in the liver. The kidneys revealed 'cloudy swelling' in all the cases, but in Case VII there was also a moderate grade of chronic interstitial nephritis.

Identification of B. influenzae of Pfeiffer. The bacilli from these cases were delicate, polar-staining, Gram-negative, and non-motile. They stained poorly with the ordinary laboratory stains, but very well with a dilute carbol-fuchsin solution if heated to the steaming point. They grew only in the presence of haemoglobin, and on human blood agar the colonies were like fine drops of dew. These remained discrete, and produced no change in the surrounding medium. Old cultures and transplants showed the characteristic varieties of involution forms.

Discussion.

Pfeiffer's bacillus has often been isolated from the respiratory tract in a variety of diseases. Thus, during an inter-pandemic period Lord (8), of Boston, found it in 33 per cent. of cases of pulmonary tuberculosis, in 39 per cent. of scarlet fever patients, in 60 per cent. of those suffering from diphtheria, in 19 to 78 per cent. of cases of measles, in 100 per cent. of cases of varicella, and in 10 to 19 per cent. of normal individuals during the same period. We feel, however, that we are justified in calling Pfeiffer's bacillus the cause of the acute generalized bronchiolitis and broncho-pneumonia in the nine fatal cases described. It was the predominant organism in the sputum during life, and it alone (except in one case where there was heavy contamination with air organisms) was grown from the terminal bronchi. And, finally, two of the cases at post-mortem showed acute endocarditis caused by *B. influenzae,* and in one of these the blood-culture was positive for this organism.

The small shotty areas of peribronchial pneumonia, which we saw, were apparently identical with the 'miliary pneumonia' which Hübschmann described as being caused by Pfeiffer's bacillus.

We wish to lay stress on the fact that, although the terminal bronchioles may contain *B. influenzae* alone, the larger bronchi in addition may contain other organisms as well, such as *Staphylococcus albus,* the pneumococcus, &c. In view of this fact, it seems to us important to make cultures from the smallest bronchi possible in cases of broncho-pneumonia.

Our cases were apparently very similar to those of 'purulent bronchitis'

described by Hammond, Rolland, and Shore (5), and by Abrahams, Hallows, Eyre, and French (1), although we have perhaps been able to show more definitely the part played by Pfeiffer's bacillus in its causation.

Although bronchiectatic cavities were rarely found in our cases, had the patients lived longer it is very probable that these would have been produced more frequently. None of the cases showed small peribronchial abscesses seen with the naked eye, but we wish to draw attention to a change in the character of the sputum which may lead one to make the diagnosis of a small abscess which has ruptured into a bronchus. This sign was noted in a case of bronchiolitis in France during the first wave of the pandemic of influenza of 1918, but its significance was not realized until the autopsy was performed. On three subsequent occasions, twice in France in the summer of 1918 and once in England during the winter of 1919–20, it was noted and the value of the sign appreciated. In all these four cases the sputum consisted of nummular greenish-yellow mucopurulent masses and no blood. Later, two or three days before death, besides these masses described above, two or three were seen in the cup of the same size, but of a brownish, brick-red colour; i. e. pus with blood intimately intermixed. At the autopsies of all these cases, one or several small abscesses, up to the size of an olive, were found to have ruptured into a small bronchus. They contained a little of the same brick-red material which had been spat up by the patient.

In 1916 and 1917 we were not in a position in France to have sections cut of the lungs, but we wish to express our thanks to Dr. A. G. Gibson of Oxford for having this done in the case of patient II.

Summary.

1. At present there are four theories as to the cause of influenza, but none of these has been shown conclusively to be true.

2. During a pandemic wave, as it attacks such large numbers of the population, influenza is easily diagnosed.

3. As the cause is not definitely known we cannot diagnose influenza during inter-pandemic periods.

4. Nine fatal cases of bronchiolitis and broncho-pneumonia, due to *B. influenzae* of Pfeiffer, which were seen at a base hospital in France in 1916–17, are described.

5. Great dyspnoea, marked cyanosis, rapid pulse, irregular temperature, the expectoration of large amounts of nummular sputum, and signs of a generalized bronchiolitis (with or without signs of consolidation), were characteristic of the disease.

6. The diagnosis rested ultimately on the finding of Pfeiffer's bacillus as the predominating micro-organism in the sputum.

7. At the post-mortem examination the most characteristic feature was a generalized bronchiolitis and 'miliary pneumonia'.

8. At autopsy this organism was grown in pure culture from the terminal bronchi, and no other organisms were seen here, though various bacteria were found in the exudate of the larger bronchi.

9. Two cases showed acute endocarditis due to *B. influenzae*, and in one of these the blood culture was also positive for the same organism.

10. These cases did not occur in the form of an epidemic, but apparently were sporadic ; they were relatively infrequent as compared with a large number of cases of lobar and broncho-pneumonia treated in the hospital ; and the clinical picture was not simulated by any of these latter cases.

11. The relation of this disease to 'purulent bronchitis' and bronchiectasis is discussed.

12. A change seen in the sputum of four patients (not included in the series) is described, and its significance for the diagnosis of a small abscess, which has ruptured into a bronchus, is set forth.

Brief Summary of Cases with Post-mortem Findings and Bacteriology.

Case I. Driver H. F., aged 30, admitted on second (?) day of disease with diagnosis of '?lobar pneumonia'. Onset gradual. Examination revealed a generalized capillary bronchitis with a patch of consolidation in the left upper lobe. The sputum was copious, nummular, and muco-purulent. Diagnosis: broncho-pneumonia. Died on tenth (?) day. Temp. high, remittent; P. 92–160; R. 24–58. P.M.: broncho-pneumonia bilateral, confluent in left upper lobe. Smears and cultures from terminal bronchi showed *B. influenzae.*

Case II. Pte. G. A., aged 37, admitted on sixth (?) day of disease with diagnosis 'P. U. O.' Onset gradual. Prev. hist. 'colds', pneumonia 1915. Examination showed generalized capillary bronchitis. Sputum muco-purulent. Diagnosis: broncho-pneumonia. Died on twelfth (?) day. Temp. chart lost. P.M.: purulent pericarditis, emphysema, cut surface of lung like young tubercles. *B. influenzae* in smears from pericardium. Smears and cultures from terminal bronchi showed *B. influenzae.* No tubercle bacilli found in smears or microscopic sections.

Case III. Pte. J. C., aged 24, admitted on eighth (?) day of disease with diagnosis of 'bronchitis'. Onset rapid. Examination: generalized capillary bronchitis, patch of dullness right lower lobe. Sputum nummular (*B. influenzae*). Diagnosis: broncho-pneumonia (*B. influenzae*). Temp. high, continued; P. 108–160; R. 28–56. Died twelfth (?) day. P.M.: dilated right heart, small areas of broncho-pneumonia, cut surface like young tubercles. Smears and cultures from terminal bronchi, *B. influenzae.*

Case IV. Pte. D. H., aged 39, admitted on third day of disease with diagnosis of 'bronchitis'. Onset gradual. Prev. hist. 'bronchitis'. Examination: consolidated right lung and part of left lower. Sweats and subnormal temperature. Sputum on twelfth day nummular (*B. influenzae*). Diagnosis: sixth day lobar pneumonia, twelfth day broncho-pneumonia (*B. influenzae*). Temp. third to sixth day, 103°–99°; later never above 99·4° and generally subnormal; P. 100–156; R. 24–52. P.M.: confluent broncho-pneumonia bilateral.

Dilated right heart, old syphilitic aortitis, acute aortic valvular disease. *B. influenzae* in cultures from terminal bronchi, aortic vegetations, and heart's blood, and in smears from vegetations.

Case V. Pte. H. C., aged 31, admitted on fourth day of illness with diagnosis of 'P. U. O.' Onset gradual. Prev. hist. rheumatic fever, 1915. Examination: generalized capillary bronchitis. Sputum nummular (*B. influenzae*). Diagnosis: broncho-pneumonia (*B. influenzae*). Died tenth day. Temp. 104°–99·3°; P. 112–144; R. 20–52. P.M.: emphysema, broncho-pneumonia bilateral, dilated right heart. Smears from terminal bronchi, *B. influenzae*.

Case VI. Pte. R. B., aged 38, admitted on sixteenth (?) day of disease with diagnosis of 'P. U. O.' Onset gradual. Prev. hist. 'influenza', 1901. Examination: generalized capillary bronchitis, dullness right upper lobe behind. Sputum: smears showed *B. influenzae*. Diagnosis: broncho-pneumonia (*B. influenzae*). Died on twenty-first (?) day. Temp. generally 101°–102°; P. 120–136; R. 24–44. P.M.: broncho-pneumonia bilateral, bullous emphysema, dilated right heart. Smears and cultures from terminal bronchi, *B. influenzae*.

Case VII. W. C., aged 44, admitted fourth day of illness with diagnosis of broncho-pneumonia. Onset rapid. Prev. hist. 'winter colds'. Examination: generalized capillary bronchitis. Sweats, 'septic' temperature. Sputum nummular (*B. influenzae*). Diagnosis: broncho-pneumonia (*B. influenzae*). Died sixth day. Temp. remittent to 103°, subnormal for twelve hours before death; P. 110–140; R. 32–52. P.M.: broncho-pneumonia bilateral, dilated right heart, acute aortic and mitral disease, myocarditis, septic spleen. Terminal bronchi, smears, and cultures, *B. influenzae*. *B. influenzae* from vegetations. Blood culture negative.

Case VIII. Pte. J. da S., aged 24, admitted eighth day with diagnosis of 'bronchitis'. Onset gradual. Prev. hist. 'bronchitis'. Examination: generalized capillary bronchitis; leucocytes 22,400. Sputum nummular (*B. influenzae*, a few pneumococci). Diagnosis: broncho-pneumonia (*B. influenzae*). Died sixteenth day. Temp. 99·5°–103·7°, last two days 100°; P. 104–150; R. 26–44. P.M.: emphysema, broncho-pneumonia bilateral, atelectasis. Dilated right heart. Terminal bronchi, cultures *B. influenzae*; secondary bronchi, *B. influenzae*, also *Staphylococcus albus*.

Case IX. Rfmn. J. P., aged 21, admitted on eleventh day of disease with diagnosis of 'bronchitis and albuminuria'. Onset gradual. Prev. hist. measles, varicella, and scarlet fever. Examination: generalized capillary bronchitis, patchy consolidation left lung, leucocytes 21,000. Sputum nummular, a few catarrhalis and pneumococci; *B. influenzae* in pure culture on twelfth day. Diagnosis: broncho-pneumonia (*B. influenzae*). Died fifteenth day. Temp. 100°–102·6°; P. 116–152; R. 30–52. P.M.: emphysema, broncho-pneumonia bilateral, atelectasis, dilated bronchiole filled with pus. Terminal bronchi, smears, and cultures *B. influenzae*, but plates heavily contaminated with air organisms.

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SPIROCHAETOSIS ICTERO-HAEMORRHAGICA
(FORMERLY KNOWN AS WEIL'S DISEASE)
A CLINICAL ANALYSIS OF FIFTY-FIVE CASES[1]

By J. A. RYLE

Part I. Introductory.

Section 1.—General. During the summer and autumn of 1916 there occurred among the British troops occupying the Ypres sector of the Western Front a small epidemic of spirochaetosis ictero-haemorrhagica. Cases also appeared among the Belgian and French troops, and later reports of scattered outbreaks affecting both allied and enemy forces have established it, in common with many other infective disorders, as essentially a war disease. The epidemic, so far as the British army was concerned, was confined to the forward trench-zone in the near neighbourhood of Ypres, a few sporadic cases only appearing among units which had recently left that area for service elsewhere. It seems certain that a few cases of the disease had been observed in the previous winter (1915–16) at the base hospitals, but none of these were experimentally confirmed.

The epidemic was investigated by Capt. Adrian Stokes, D.S.O., R.A.M.C., the officer in charge of No. 1 Mobile Laboratory; Capt. J. A. Ryle, R.A.M.C., officer in charge of medical wards at No. 10 Casualty Clearing Station, the writer of this paper; and Major Tytler, R.A.M.C., who was assisting Capt. Stokes. By numerous experiments which were reported in a preliminary communication to the *British Medical Journal*, September 23, 1916 (1), and to the *Journal of the Royal Army Medical Corps* for September, 1916 (1), and at greater length in *The Lancet*, January 27, 1917 (2), they were able to prove the nature of the disease, to confirm the work already carried out by Inada and his collaborators in Japan during 1914 and 1915 (3), and to establish beyond dispute the existence of a non-icteric type of the infection. Their reports were based on observations of about 100 cases, 50 of which had been under the direct care of the writer. The total figure of the epidemic cannot be estimated, since a considerable number of cases (owing to unfamiliarity with the disease and especially with its non-icteric type) must have passed undiagnosed through various medical units. Probably, however, the total of cases did not greatly exceed 200.

[1] This communication, with the addition of 55 case-reports and charts, and historical and pathological references, was accepted as a Thesis for the Degree of Doctor of Medicine in the University of London, July, 1919.

[Q. J. M., Jan., 1921.]

Recent researches into spirochaetosis ictero-haemorrhagica in all countries have been conducted mainly along epidemiological and pathological lines, and so thorough and successful have they been that an amplification and completion of the picture from the clinical point of view would appear to be almost the sole remaining duty of its students. A moderately full clinical summary was included in the paper by Stokes, Ryle, and Tytler (2), while Dawson and Hume (4), in the course of a discussion of infective jaundice generally, dealt at some length with the special features of the spirochaetal infection. There does not, however, appear to exist a recent and comprehensive study dealing primarily with the clinical aspects and variations of this disease. With a view to making good this deficiency, and prompted also by a personal experience of the diagnostic difficulties (the diagnosis during the first week of infection and frequently afterwards is still dependent on clinical evidences), as well as by certain new conceptions and the inadequacy of the older accounts, the writer has collected and submitted to analysis and discussion his own medical records of the epidemic. Where, for military or other reasons, individual records have lacked completion he can claim the support of lasting impressions based not only on the vivid characteristics of the disease itself, but also on the general associations of the epidemic, and in particular on the happy co-operation between the ward and the laboratory for which it was responsible.

Section 2. Epidemiological and aetiological features. Weil recognized that the disease occurred in localized groups and epidemics, and found it common among butchers. Other writers of the same and later periods noted a liability to infection among workers in sewers and slaughter-houses and wet ditches, a liability which is now readily explained by the incrimination of the rat. Judging from the literature, as well as from recent experience, this tendency to a local or group epidemicity is the common experience.

According to Osler, 'Local and widespread outbreaks of jaundice have been known for years. Three or four cases may occur in one house, or many persons in one institution are attacked, or the disease becomes widespread in a community. In Great Britain this epidemic form is rare. In the United States many outbreaks have occurred' (8). Epidemics have been reported from Syria, Greece, Egypt, India, and from South Africa during the Boer War (8). In Japan the disease seems to have been endemic. In the course of the war outbreaks occurred in Belgium and France and on several other fronts, but the jaundice which prevailed during the Gallipoli campaign has been regarded as belonging probably to the 'enteric group' rather than to the spirochaetal type of infection. Climate and nationality may be held to play little or no part in controlling the incidence of epidemics.

Inada and his colleagues state that their cases occurred in the wet shafts of mines, that men working in the dry shafts were not affected, and that when the wet shafts were pumped out on their advice the incidence diminished. Stokes in searching for a seasonal variation found that the case-incidence increased after a wet spell and decreased after dry weather; he was also able, with the aid

of 'spot maps', to localize the infected area to two particular sectors of trench, which were wet and ill-drained owing to the nature of the ground, and did not become properly dry even in fair weather. In the series described hereafter it is worthy of note that there are no officers, and in the whole course of the investigation there was only one instance of an officer becoming infected; the men who had to occupy outlying water-logged posts more frequently and for longer periods developed the disease either in or shortly after leaving the trenches.

Moisture appears therefore to play a definite part in the aetiology. The bulk of the cases in this series occurred between April and October, but although rare later, they did not entirely disappear during the winter months, so that summer temperature cannot be a necessary factor. A German writer has recently shown that the spirochaetae are not killed by freezing (9). In view of the greater prevalence in wet places and warm weather, and the close clinical resemblance to yellow fever, the possibility of insect 'carriers' had to be considered. *Stegomyia fasciata* does not exist in Belgium, and the men gave no history of being bitten by gnats or mosquitoes, although *Culex* and *Anopheles* are both plentiful in the neighbourhood of Ypres, and the writer has found *Culex* in sheltered spots in northern Flanders even in the colder months. Stokes was unable to transmit the disease to guinea-pigs by lice with any of the ingenious means adopted, and it is probable that the epidemic would have assumed far larger proportions if the louse had been the intermediary.

In 1916 the Japanese succeeded in finding spirochaetae in the kidneys and urine of 38 per cent. of ordinary field-rats. Stokes confirmed this work and found a high proportion of infected rats in the two sectors of trench from which the majority of cases came. He also showed that guinea-pigs infected by rats' spirochaetae could be cured by the serum of a convalescent human patient.

The rat therefore stands convicted as the 'carrier', and Nicolle and Lebailly (10) have recently shown that the virus can be conserved, without illness, in mice as well as rats. There is little doubt that the infection is disseminated by means of the urine, and the only uncertain link in the chain is the actual path of infection.

Guinea-pigs can be infected by inoculation, feeding, or through the intact skin, but it is not established by what route the infection occurs in man. Both Weil and Inada favoured the alimentary route. Certainly in Flanders, whether they drank shell-hole water or not, it is beyond dispute that men continually ate food contaminated by mud and water from the trenches in which they lived. Their skins, however, were equally exposed to the infective medium and abrasions were common. There is no evidence that rat-bites were ever the cause of the infection, although the rats were notoriously bold and known even to steal food from the men's pockets while they slept. A German observer (9) states that gastric juice kills pure cultures of the spirochaetae in twenty minutes, but this laboratory evidence alone can hardly be held to negative the alimentary theory.

By the discovery that the rat harbours the infection the world-wide distribution, the influence of wet, and the increased epidemicity in times of war are all explained. It is improbable that age and sex have any particular effect on

the incidence, the occurrence among males of military and working age being obviously due to their exposure to the conditions which favour infection.

The absence of any further epidemics on the Western Front has been attributed by some to the great increase in the use of gas. The opinion certainly gained ground that, following the systematic employment of offensive gas, there was a marked diminution in the number of rats in the forward area.

Part II. Records, Analyses, and Description.

The fifty-five cases on which the subsequent discussion is based were all under the personal care of the author at No. 10 Casualty Clearing Station, and were admitted to his wards during the period May, 1916–January, 1917. They were nursed in a hospital-hut containing twenty to twenty-five beds set aside for the severer medical admissions. No attempt was made to segregate the patients, but instructions were given to the Sister and orderlies to carry out the usual precautions with regard to utensils and excreta adopted in the case of typhoid patients. No ward-infections occurred, nor, in the light of recent knowledge, were they to be expected. Brief clinical notes and copies of charts were entered in a note-book, and with the exception of a few minor emendations these stand unaltered in the records forming the basis of this paper.

The diagnosis of all cases was initially clinical; in 23·6 per cent. it was confirmed by animal experiment. In a few instances the diagnosis might seem to rest on slender evidences, but actually very great care was taken to exclude not only cases of jaundice due to other causes, but also in the non-icteric types to differentiate from the other febrile war-diseases. Previous to the commencement of the epidemic the writer had had more than a year's continuous experience of war-fevers, and had been almost daily confronted with the problems entailed in the differentiation of obscure pyrexial conditions, nor during the course of the epidemic did he cease to have under observation cases of trench fever and other pyrexial maladies for comparison and contrast. Furthermore, the accessibility of laboratory controls and the exposure to laboratory criticism acted as a constant stimulus to diagnostic caution and accuracy. Blood-cultures for the elimination of 'enteric group' infections were undertaken in 16 per cent. of the series. Lack of space has necessitated the omission of all individual case-reports and charts. Representative charts were published in the original articles by Stokes and Ryle (1).

Section 1. Analytical Tables.

TABLE I.*

Case.	Jaundice.	Animal Experiment.	Day.	Pyrexia.
				°
1	+	+	6th	102[4]
3	+	−	6th	102
4	+	+	6th	100[6]
6	+	−	6th	100[4]
7	+	−	7th	101
8	+	−	7th–8th	99–101
9	+	+	?	101[6]
10	+	−	7th	100[2]
11	+	+	5th–6th	99[6]–103[2]
12	+	−	?	97–98
13	+	+	5th	99[4]
14	+	−	6th	102[4]
15	+	+	6th	103[4]
16	+	+	4th	102[2]
19	−	−	7th	99–101
29	−	−	5th	102
31	−	−	2nd	105
34	+	+	4th	102
35	+	+	4th	100
36	−	+	5th	100
49	−	+	6th	102
50	−	+	2nd	103[4]
55	−	+	4th	103[4]

TABLE II.

A. Results in Relation to Day of Experiment.

	+	−	percentage +.
2nd day	1	1	50
3rd day	No inoculations		
4th day	4	0	100
5th day	3	1	75
6th day	4	3	57
7th day	0	4	0

(One positive and one negative result were obtained on uncertain days)

B. Results in Relation to Day of Experiment (Stokes's Series).

	+	−	percentage +.
1st day	0	1	0
2nd day	1	1	50
3rd day	1	0	100
4th day	9	0	100
5th day	6	8	42·8
5th or 6th day	2	0	100
6th day	5	6	45·4
7th day	2	2	50
8th day	0	3	0
9th day	0	3	0

* Showing results of animal inoculations in 23 cases, day of disease on which inoculation was performed, and highest pyrexia on that day.

SUMMARY.

Of 16 cases with jaundice { 9 were positive = 56 %. 7 were negative = 44 %.

Of 7 cases without jaundice { 4 were positive = 57 %. 3 were negative = 43 %.

In 30 cases no animal experiment was performed.

In 2 cases an experiment was performed but the reports are missing.

In 4 cases with jaundice and 5 cases without, haemo-culture in bile-salt medium gave a negative result.

Table III.

Showing the Recorded Incidence of 10 Important Manifestations and the Severity in each of 55 Cases.

Case.	1 Jaundice.	2 Albumin.	3 Acetone.	4 Herpes.	5 Haemoptysis.	6 Epistaxis.	7 Conjunct. Injection.	8 Vomiting.	9 Abdominal Pain.	10 Limb Pains.	Severity.
1	+	+	...	+	+	+	+	..	+	+	severe
2	+	+	+	...	...	...	+	+	...	+	fatal
3	+	...	...	...	...	...	+	+	+	+	severe
4	+	+	...	...	...	+	+	+	+	+	severe
5	+	...	...	...	...	...	...	+	..	...	slight
6	+	+	...	...	+	+	+	+	+	...	very severe
7	+	+	...	+	...	...	+	+	...	...	mod. severe
8	+	+	...	+	...	...	+	...	...	+	severe
9	+	...	...	...	...	...	+	...	...	...	fatal
10	+	...	...	+	...	+	+	+	...	+	severe
11	+	+	...	...	...	...	+	+	+	+	mod. severe
12	+	...	+	...	...	...	...	+	...	+	slight
13	+	...	...	...	...	...	...	...	...	...	slight
14	+	+	+	...	...	...	+	...	...	...	severe
15	+	+	+	...	...	...	+	...	...	...	severe
16	+	...	...	+	+	...	...	+	...	...	severe
17	+	...	...	...	...	...	+	...	...	+	slight
18	+	...	...	...	...	...	...	...	...	+	slight
19	–	...	...	+	...	...	+	+	...	...	slight
20	+	+	...	...	...	...	...	+	...	+	mod. severe
21	–	+	...	...	...	...	...	+	...	+	severe
22	+	+	...	...	...	+	...	+	...	+	mod. severe
23	+	+	+	+	...	...	...	+	...	+	severe
24	+	...	...	...	...	...	...	+	...	...	mod. severe
25	+	...	...	+	...	...	...	+	...	+	mod. severe
26	+	+	...	+	...	...	...	+	...	...	slight
27	+	+	+	+	...	...	...	+	...	...	severe
28	+	+	...	...	...	...	...	+	...	...	slight
29	–	+	+	+	+	...	...	+	...	+	mod. severe
30	+	...	...	+	...	...	...	+	...	...	slight
31	–	+	+	...	+	+	...	...	...	...	very severe
32	+	...	...	...	+	...	...	+	...	...	slight
33	+	...	...	...	...	...	...	+	...	+	slight
34	+	+	...	...	...	...	...	+	...	+	severe
35	+	+	+	+	...	...	...	+	...	...	very severe
36	–	...	...	+	+	...	...	+	...	...	slight
37	+	+	...	+	...	...	...	+	...	...	slight
38	+	...	...	+	+	...	...	+	...	...	severe
39	–	...	...	+	...	...	+	+	...	...	mod. severe
40	+	+	...	...	...	...	...	...	...	...	slight
41	–	...	...	+	...	...	...	...	...	+	mod. severe
42	+	+	...	+	+	...	+	+	+	...	very severe
43	–	+	...	...	+	...	+	+	...	...	very severe
44	+	+	...	+	+	...	...	+	...	...	severe
45	+	...	...	+	...	+	...	+	...	+	fatal
46	+	+	...	+	...	...	...	...	...	...	mod. severe
47	+	+	...	+	+	...	...	+	...	+	mod. severe
48	–	+	...	...	+	+	+	+	+	+	very severe
49	–	...	...	...	...	...	+	...	...	+	slight
50	–	+	...	...	+	...	+	+	...	+	severe
51	–	...	...	+	...	+	...	+	...	...	mod. severe
52	–	+	...	...	...	...	+	+	...	...	slight
53	–	...	...	+	...	...	...	+	...	...	severe
54	+	+	...	+	+	...	+	+	...	...	severe
55	–	+	...	...	...	...	...	+	...	...	severe

Under the non-icteric heading are included one case (52) with bile in the urine but no coloration of skin or conjunctivae, and one in which there was a questionable tinge to the conjunctivae late in the acute stage.

Under 'conjunctival injection' are classed also 'injected eyes', 'sore eyes', and two cases only noted in the case-report as 'photophobia'.

Summary of Table III.

Cases with jaundice 40 = 72·7 %.
Cases without jaundice 15 = 27·3 %.

Albuminuria is recorded in:—
24 (or 60 %) of jaundiced cases.
8 (or 53·3 %) of non-icteric cases.
32 (or 58·1 %) of total cases.

Acetonuria is recorded in:—
7 (or 17·5 %) of jaundiced cases.
2 (or 13·3 %) of non-icteric cases.
9 (or 16·3 %) of total cases.

Herpes labialis is recorded in:—
18 (or 45 %) of jaundiced cases.
6 (or 40 %) of non-icteric cases.
24 (or 43·6 %) of total cases.

Haemoptysis is recorded in:—
9 (or 22·5 %) of jaundiced cases.
7 (or 46·6 %) of non-icteric cases.
16 (or 29 %) of total cases.

Epistaxis is recorded in:—
6 (or 15 %) of jaundiced cases.
3 (or 20 %) of non-icteric cases.
9 (or 16·3 %) of total cases.

Conjunctival injection is recorded in:—
15 (or 37·5 %) of jaundiced cases.
7 (or 46·6 %) of non-icteric cases.
22 (or 40 %) of total cases.

Vomiting is recorded in:—
30 (or 75 %) of jaundiced cases.
12 (or 80 %) of non-icteric cases.
42 (or 76·3 %) of total cases.

Abdominal pain is recorded in:—
6 (or 15 %) of jaundiced cases.
1 (or 6·6 %) of non-icteric cases.
7 (or 12·7 %) of total cases.

Limb pains are recorded in 24 = 43·6 o total cases.

Classification according to Severity.

A. Jaundiced cases.

slight	moderately severe	severe	very severe	fatal
12 = 30 %	8 = 20 %	14 = 35 %	[3 = 7·5 %	3 = 7·5 %]
			15 %	

B. Non-icteric cases.

slight	moderately severe	severe	very severe	fatal
4 = 26·6 %	4 = 26·6 %	4 = 26·6 %	3 = 20 %	0 = 0 %

C. Total Cases.

slight	moderately severe	severe	very severe	fatal
16 = 29 %	12 = 21·8 %	18 = 32·7 %	6 = 10·9 %	3 = 5·4 %

TABLE IV.

The Pyrexia.

1	2	3	4	5	6
Case.	Maximal Excursion recorded.	Day of Recording.	Duration of Initial Pyrexia.	Relapse.	Recrudescence.
	°				
1	102^4	6th	11	—	—
2	100^6	10th	14 (died)	—	—
3	102	6th	9	—	12th day
4	101	7th	14	—	—
5	99^2	10th	10	—	—
6	100^4	6th	11	14th–22nd day	—
7	101	7th	10	—	—
8	103^2	2nd	13	—	—
9	101^8	?	? (died)	—	—
10	100^2	7th	10	—	—
11	103^2	7th	11	—	—
12	98^2	? 6th	?	—	—
13	99^4	5th	10	—	—
14	102^4	6th	12	—	—
15	103^4	6th	10	—	—
16	103	5th	9	—	—
17	102^2	?	?	—	—
18	100	8th	10	—	—
19	101	8th	11	—	—
20	102	?	?	—	—
21	102	9th	?	—	—
22	102	8th	11	—	—
23	99	7th	9	—	14th–17th day
24	103^4	6th	11	—	—
25	102^2	9th	12	—	—
26	101^6	6th	9	—	—
27	101^2	6th	14	—	—
28	100^8	11th	13	—	—
29	102^8	6th	8	—	—
30	99^2	9th	6	—	9th day
31	105	2nd	10	—	—
32	102	6th	9	—	—
33	98^4	7th	?	—	—
34	102	4th	13	—	10th–13th day
35	102	3rd	6	—	9th–14th, 16th–19th days
36	100^4	6th	7	—	—
37	100^6	8th	10	—	—

TABLE IV (*continued*).

1	2	3	4	5	6
Case.	Maximal Excursion recorded. °	Day of Recording.	Duration of Initial Pyrexia.	Relapse.	Recrudescence.
38	103^{6}	3rd	10	—	10th–12th day
39	101	7th	9	—	10th–12th day
40	99	?	?	—	—
41	103^{6}	2nd	8	—	—
42	104^{2}	3rd	8	—	—
43	104	4th	12	—	—
44	102^{4}	5th	11	—	—
45	102	3rd	8 (died)	—	—
46	104^{2}	3rd	9	—	10th–14th day
47	101^{2}	6th	10	16th–22nd day	—
48	104	6th	12	—	—
49	102	6th	9	—	—
50	103^{4}	2nd	?	—	—
51	104	3rd	8	—	—
52	103^{2}	3rd	8	—	—
53	103^{2}	6th	9	—	—
54	103^{6}	7th	16	—	—
55	103^{2}	4th	10	—	—

[For summary of Table IV, see Part II, Section 2 (c), The Fever.]

TABLE V.

Showing (i) *Maximal Recorded Pyrexia in Acute Phase of the Disease and Day of Occurrence;* (ii) *Average Maximal Recorded Pyrexia of Acute Phase for each of the First 10 Days.*

Day of Disease.	Maximal Recorded Pyrexia of Disease. °	Average Maximal Pyrexia of Disease. °
2nd	105	103^{8}
3rd	104^{2}	103
4th	104	103^{3}
5th	103	101^{6}
6th	104	102^{1}
7th	103^{6}	100^{9}
8th	102	100^{9}
9th	102^{2}	101^{1}
10th	100^{7}	99^{9}

The maximal temperature recorded occurred:—

On the	1st	day	in 0 cases
	2nd	,,	,, 4 ,,
	3rd	,,	,, 7 ,,
	4th	,,	,, 3 ,,
	5th	,,	,, 3 ,,
	6th	,,	,, 16 ,,
	7th	,,	,, 8 ,,
	8th	,,	,, 4 ,,
	9th	,,	,, 3 ,,
	10th	,,	,, 2 ,,

[For discussion of Tables IV and V, see Part II, Section 2 (c), The Fever, and Part III, Section 2 (f).]

The reason for the frequency of occurrence of the maximal pyrexia on the 6th and 7th days in this series is largely due to the fact that the majority of the cases were not admitted until this stage. The average time before admission was 5·5 days. It will be seen in Table V that the average maximal pyrexia occurs on the 2nd, 3rd, and 4th days.

Section 2. Description.

(*a*) *Period of incubation and the group incidence.* It was impossible to form any definite conclusions from the clinical evidences alone as to the length of the incubation period. The fallacies in the accounts given by the patients relating to their tour of duty in the trenches and dates of indisposition were too numerous, and in the severer cases the mental and physical condition on admission often precluded exhaustive inquiries. In Case 45, assuming the seventeenth to be the last possible day of infection, as that was the day on which he left Ypres to go on leave, and the twenty-ninth to be the day of acute inception, twelve days would be the estimated incubation period. Owing to the complication of a septic hand it is difficult more accurately to determine the day of onset, but from the twenty-ninth onwards there is a history of those generalized pains which are so characteristic of the disease. In Case 7 there was a history of drinking water from a foul pond in the preceding week. Assuming this to have been the occasion of an alimentary infection the incubation period would be less than fourteen days. In Case 9 there was a history of duty in isolated posts and a probable use of shell-hole water between May 30 and June 6. The onset was on or about June 11, which suggests a minimum period of five, and a maximum period of twelve days' incubation. In an accidental laboratory infection recorded by Martin and Pettit (5) the incubation period was shown definitely to be between six and eight days. It is probably subject to variations according to the virulence or dosage of organisms.

The cases quoted above, Nos. 7, 9, and 45, were (with the exception of No. 5, who also attributed his onset to the drinking of some water because it was followed an hour later by bilious vomiting) the only cases in which there was any specific suggestion as to a possible path of infection. In four cases there was a history of a period of malaise preceding the acute inception. Case 17 said he 'had had fever for a week, but had felt unwell for a week before that'. Case 20, although he was obviously in the early acute stage on admission, and did not develop jaundice until after admission (the jaundice usually appears between the third and sixth days), stated that he had been ill for a fortnight. Case 45 stated that he felt generally 'run down' during his leave, which included the period of incubation, but he had a mildly septic hand at that time. Case 50 described a sudden onset after a few days of malaise. These histories suggest that there may be a period of invasion before the septicaemia becomes established in which subjective sensations are experienced though actual signs of a general infection are absent.

As indicating the group occurrence of infections it is interesting to note that

four cases were admitted from the same unit in one instance, three from one unit in two, and two from one unit in three instances. Furthermore, by following the records serially in order of admission, it is quite easy to tell with accuracy the divisions which were holding the line in the Ypres sector at the different periods of the epidemic.

(*b*) *The onset.* The notes record or suggest a sudden onset in 14 cases, and a gradual onset in 6 cases. In the remaining 35 cases the mode of onset is not specified, but the impression left by the epidemic is that sudden onset is a very definite characteristic of the disease.

In two cases (5, 6) it was described as 'sudden with vomiting': Case 4 reported that he was found unconscious in a latrine: Case 33 described an onset with giddiness and pain in the limbs, and Case 34 'woke up with bad pain in the limbs'. The two last mentioned represent the most usual form of reply to inquiries as to first symptoms. Giddiness, headache, and pains all over, but especially referred to the limbs, may be regarded as constant initial manifestations. Loss of appetite and vomiting and a feeling of great weakness are almost universally complained of in the acute stages.

(*c*) *The fever.* Owing to the fact that cases were not (taking an average) sent in for admission until the fifth or sixth day of illness, early records of the pyrexial curve are not so numerous as could be wished. There are, however, among the records three charts which include the first, and six which include the second day of disease.

The chief characteristics of the fever are as follows: There is a steep or swinging ascent from the first day, reaching a maximum on the second, third, or fourth day of illness (see Table V), or occasionally later. After this there is a descent by irregular lysis with big remissions. Variability in type and conformation of the chart and the wide limits of the diurnal variation are perhaps the most striking features. The initial pyrexia lasts on the average ten days, and is followed by a period during which the temperature remains subnormal, often markedly so, lasting from one to six days. There is a distinct tendency to relapse, or to small pyrexial recrudescences. Two relapses lasting from the fourteenth to the twenty-second (eight days) and from the sixteenth to the twenty-second (six days) are recorded in this series, but it was frequently necessary to evacuate cases to the base almost immediately after the primary fall of temperature, and there is reason to suppose that the actual incidence of relapse is considerably higher than these figures indicate. The relapse does not appear to be necessarily accompanied by a return of the jaundice or other graver stigmata.

There are in this series two 'one-day' recrudescences on the ninth and twelfth days respectively; two 'two-day' recrudescences from the tenth to twelfth days; two 'three-day' recrudescences from the tenth to thirteenth and fourteenth to seventeenth days; and one 'four-day' recrudescence from the tenth to fourteenth day. One case showed two recrudescences from the ninth to fourteenth and sixteenth to nineteenth days respectively.

Classifying relapses and recrudescences together it is found that they occur

in 18 per cent. of all cases. Generally speaking, the non-icteric cases were evacuated rapidly, but it is perhaps of interest that while under observation none of these relapsed, while only one had a small and pyrexial recrudescence. The possible significance of this is discussed in Part III, Section 2 (f), below.

The longest initial pyrexia recorded is of sixteen days' duration ; the shortest is six days. The average initial pyrexial period is ten days. The longest record of fever including periods of relapse is twenty-two days.

The highest recorded temperature is 105° on the second day of disease. The lowest recorded temperature is 96° on the ninth day in a case which recovered, and in one case during the collapse stage preceding death. A steep 'collapse' descent to subnormal was shown in two of the fatal cases (2, 9), while in the third there is a persistently subnormal temperature for five days preceding death.

In several cases (e. g. 16, 29, 39, 42, 44, 46, 48) a steep fall—described hereafter as the 'critical fall'—of temperature occurred on the seventh, eighth, or ninth day of the disease, and was sometimes associated with an amelioration in symptoms, though the pyrexia did not necessarily settle immediately to normal. Its possible significance is discussed in Part III, Section 2 (f).

The maximal and average maximal temperatures of the disease in relation to the day of disease are shown in Table V. Their relationship to other evidences of the septicaemic state is discussed in Part III, Section 2 (f).

Other clinical evidences of fever, apart from thermometric records, are in the early stages a hot skin and a malar flush, and in all cases throughout the period of pyrexia an intense desiccation of the tissues which is described hereafter. No rigors were recorded.

(*d*) *Alimentary system.* The tongue, especially in severe cases, is brown and excessively dry, usually without a thick fur, while at times it has an almost glazed appearance. It is not infrequently fissured, and its protrusion is a slow and painful process. There are sordes on the lips and teeth, which lose the customary polish given to them by the saliva, the saliva itself appearing to be very deficient in amount. Peptic ulcers were present in one case (5), bleeding gums in one case (23), and Case 36 developed a bad stomatitis. Mastication and swallowing are difficult and only add to the febrile anorexia; the patients can seldom be persuaded to take anything more than fluids in the acute stage of the malady.

Vomiting is a very constant symptom. It is recorded in 76·3 per cent. of all cases, but probably has an even higher incidence. It occurred in 75 per cent. of jaundiced and 80 per cent. of the non-icteric cases. The vomitus is commonly bilious. Frequent and sustained vomiting is of serious significance and only occurs in the most severe cases. Haematemesis is of doubtful occurrence. Hiccough occurred in two fatal cases (2, 45) and in one extremely grave case which recovered (6).

Abdominal pain, which is generally vague and diffuse and not associated with rigidity or localized tenderness, occurred in six (= 15 per cent.) of the jaundiced cases and one (= 6·6 per cent.) of those without jaundice. Its significance is discussed in Part III, Section 2 (a), below. In one case it was severe, and

the patient preferred to lie on his stomach. There was never anything to suggest biliary colic or local involvement of the gall-bladder or ducts. Two cases gave a history of initial diarrhoea, but otherwise profound constipation was the rule throughout the disease. Meteorism analogous to the atonic meteorism of typhoid fever was never observed, and the abdomen was generally flat. The stools were by no means generally pale, and in some cases were actually bile-stained. Bowel haemorrhages were rare, occurring in one fatal case, while in one other case, in which haemorrhoids were not definitely excluded and constipation was extreme, a little blood with mucus was passed on one occasion.

Hepatic enlargement with definite tenderness was present in one case (6) with jaundice and one (48) without jaundice.

With the termination of the fever and the disappearance of the jaundice the appetite quickly returned in the majority of cases, but the constipation persisted through early convalescence.

(*e*) *Circulatory system.* The heart. In spite of the frequent severity of the disease and its septicaemic nature there is little evidence of any direct or permanent damage to the heart-muscle or valves in the cases which recover. In one case only (15) was there clinical evidence of cardiac dilatation, and this was merely a temporary manifestation confined to the acute stage of pyrexia. During the periods of observation no signs suggestive of endocarditis or pericarditis were recorded. The increased respiration rate described in the following section (excepting possibly in Case 15, where there was evidence of dilatation and a fast pulse) was in no instance associated with signs of cardiac failure; the pulse was slow in proportion to the respirations, and other evidences such as venous engorgement and cyanosis were entirely lacking. The increase in the size of the liver in the two cases in which it occurred was held to be due to hepatitis rather than engorgement. In one of the fatal cases the pulse is recorded as 96–100 on the day preceding death, and in another, although reported as 'intermittent' shortly after admission, it was counted at 96 on the day of death. In both cases, however, the heart was found to be soft, flabby, and dilated at post-mortem. In the third case the pulse was 76 four days before the fatal issue, but records for the remaining period are missing.

In all three cases there was good reason to assume that causes other than myocardial failure contributed to the fatal result.

The pulse was usually of good volume and tension throughout. In the more severe cases, such as Case 48, although not greatly increased in rate, it became weak during the height of the disease and particularly so just prior to 'the critical fall' of temperature. The rate was usually slow in proportion to the pyrexia both in the jaundiced and the non-icteric cases. Where rapid rates are recorded it is for a short period only and in the most acute phases of the disease. The maximal recorded pulse-rate is 134. The average maximal pulse-rate is 100.

Bradycardia is frequently present in the early stages of the post-pyrexial period, but is usually of short duration. The lowest rate recorded is 38. The

average minimal rate is 67 in the jaundiced cases, 61 in the non-icteric cases, and 65 for the whole series. Pulse-rates below 60 were noted in six cases (= 15 per cent.) with jaundice, and in five (= 33·3 per cent.) without. These low pulse records were usually associated with a subnormal temperature.

The maximal recorded variation in pulse-rate during the disease in the same individual is 66 beats; the minimal 4 beats.

A dicrotic pulse was noted in Case 34.

Excepting in one of the fatal cases no irregularities of the pulse were observed.

(*f*) *Respiratory system.* Epistaxis occurred in 16·3 per cent. of the series, and was slightly more frequent in the non-icteric cases. In no case of this series was it a serious symptom, though in one case described in the article by Stokes, Ryle, and Tytler, it was so serious as to necessitate plugging of the nares.

The chief evidences of pulmonary involvement were:

(i) Haemoptysis.

(ii) Increase in the respiration rate.

Cough was a minor complaint, and is only definitely recorded in three cases (8, 53, 54), though it was presumably present whenever haemoptysis occurred. Bronchitis was diagnosed in two cases (35, 42). Grunting expirations, so obvious and typical as almost to convince the observer of the presence of pneumonic consolidation, were present in several cases and are specifically mentioned in the records of Cases 42 and 43. In no single instance, however, in spite of a careful examination, could physical signs of consolidation be discovered. The probable explanation of the symptom and the absence of signs is discussed later.

Pain was definitely referred to the chest in one case only (53). Orthopnoea in association with haemoptysis and rapid respirations was present in Case 43.

The haemoptysis was of two kinds—'rusty' and 'red'. 'Rusty' sputum was the more common and closely resembled the 'rusty' sputum of a lobar pneumonia; if possible it was more viscid, but in amount it was much less. Red blood in the form of small clots was expectorated in a few cases. Profuse haemorrhage never occurred.

Dyspnoeic attacks preceded death in one case (2) in which there was also shown a curious 'catchy' type of respiration. The increase of respiration-rate referred to above attained or exceeded 24 per minute in eleven cases (20 per cent. of the series), and in six of these was accompanied by haemoptysis. The maximum recorded rates were 24 (two cases), 26, 28 (two cases), 30 (two cases), 32, 36 (three cases).

(*g*) *Excretory system.* Difficulty of micturition was occasionally noted. It is recorded in Cases 1 and 2, both bad cases. Whether it was due to a febrile atonicity of the bladder, or possibly to haemorrhage into the bladder-wall such as occurred in Case 45, or to other causes, cannot be definitely stated. Macroscopic haematuria was only present in one case (45), which ended fatally and in which bowel haemorrhages and epistaxis were also present. Red cells were found in the centrifugalized deposit in other cases (e.g. 23) and leucocytes in Case 11.

Albuminuria is recorded in 58·1 per cent. of all cases, in 60 per cent. of those with, and 53·3 per cent. of those without jaundice, but the impression gained was that, with repeated examinations and particularly in those early days which cannot be recorded in many cases on account of their late admission, it would have been found to be an even more frequent manifestation. Quantitatively the albumin varied from 'a trace' to 'large amounts'. Probably it was a simple febrile albuminuria in a large proportion of cases, but in the severe cases it was undoubtedly attributable to a nephritic condition. Casts are reported in Cases 14, 22, and 35, but were not consistently sought for; they were of the granular tube-cast variety. Bile was commonly present, though it did not darkly tinge the urine in the majority of cases. It is specially recorded in Cases 3, 22, and 52; in the last named it was detected although jaundice of the skin and conjunctivae was absent.

Acetone was demonstrated in the urines of the severe cases and is recorded in 16·3 per cent. of the total. The 'very severe' and 'fatal' cases constituted 16·3 per cent. of the series, though acetonuria was not confined to these groups. In one case (12) acetone was detected also in the breath. The significance of the albuminuria and acetonuria is discussed in Part III, Section 2 (*b*). Neither the albuminuria nor the acetonuria persisted for long in the majority of cases. No oedema of the tissues was ever observed; it is not known whether chronic renal changes ever supervene.

(*h*) *Nervous system.* The nervous manifestations are numerous. Though certain of them included hereunder, such as the general weakness and muscular impairment, should possibly be dealt with as muscular manifestations, they have, in the absence of more accurate knowledge, been grouped under the same heading as other symptoms more definitely nervous in origin. Giddiness was complained of as an initial symptom by a large proportion of all patients, and one man was found unconscious in the latrine. During the acute febrile period in all cases the general weakness is very noticeable, and in the grave cases there is extreme prostration. This prostration in some suggests a listlessness and passivity induced by sheer exhaustion, while in a greater number it is aggravated by an intense physical and mental misery due to the generalized pain and hyperaesthesia. The pain is felt in all the muscles of the body, but particularly in the limbs, and it renders the patient unwilling to undertake any unnecessary movements. Passive extension of the arm at the elbow-joint for the purpose of taking a sample of blood from the basilic vein frequently gave a sensation of muscular resistance to the observer, not met with in other diseases, and seemed to give definite discomfort to the patient. The men complain of feeling 'as if they had been beaten all over', and the muscles are found to be tender on pressure. Even the weight of the bed-clothes is occasionally resented. The pain and tenderness are principally referred to the back and limbs, and appear to be muscular or fascial rather than cutaneous; they are never unilateral or associated with a particular nerve distribution. In one case only was the pain referred to the shins, which were tender as in 'trench fever', but showed no evidence of any periosteal swelling or thickening.

Limb-pains or leg-pains are specifically recorded in 43·6 per cent. of all cases, but 'generalized pains' may be regarded as always including 'limb-pains', and so constantly were they present that a case of jaundice lacking a history or evidence of limb-pains was regarded as almost certainly of other causation. Headache was a very constant symptom, but is usually masked by the still more severe corporeal and limb pains, and so does not appear as a primary complaint with great frequency. Occasionally, however, it was sufficiently impressive to cause the admission of a patient with the label '? Cerebro-spinal meningitis'. In no case were true meningeal signs observed; neck-rigidity and a true Kernig's sign were never present.

Drowsiness is recorded in one case on admission, but probably on account of the pains it was not usual, and in fact hypnotics were not infrequently necessary. Mental confusion was present in one case (9) as a terminal feature, and in the same case restlessness and coma were observed. Restlessness and coma occurred latterly in another case (2) with a fatal ending, in which case also muscular twitchings akin to the subsultus tendinum seen in typhoid fever were present. No pareses are recorded, and it will be noticed that the nervous manifestations are for the most part sensory or associated with the toxaemic effects of the disease on the higher centres.

Special senses. The eyes. Conjunctival injection was very frequently present, and was commonly associated with tenderness on pressure over the eyeballs. Grouping together cases of 'conjunctival injection', 'sore eyes', and 'tender eyeballs' the records give a 40 per cent. incidence in all cases, but probably this is a low estimate.

Subconjunctival haemorrhages occurred in one case (39). Photophobia was present in Cases 15 and 17; and in 15, and to a less extent in 39, there was a definite pink suffused zone at the corneo-scleral margin suggesting an early irido-scleritis. There was, however, no clouding of the iris, and following treatment with a shade and atropin nothing further to indicate a true iritis developed.

Coloration of the conjunctivae preceded or accompanied the general icterus. No involvement of other organs of special sense was noticed.

(i) The spleen and lymphatics. Although diligently sought for, as it is stated to occur in the text-book accounts, enlargement of the spleen was never discovered. At all the post-mortem examinations performed the spleen was found to be small, so that the clinical findings may be regarded as accurate.

Glandular enlargement is recorded in six of the earlier cases, but it was not consistently sought for in the remainder of the series. The degree of enlargement was always slight, and the predisposing causes of adenitis in soldiers on active service are so numerous that the condition was not regarded as being of great diagnostic value. The writer is, however, of the opinion that a specific adenitis does occur in the disease.

The thoracic wall of the axillary fossa and the posterior cervical region were the usual sites for enlarged glands. The glands, which seldom exceeded a small

bean in size, are discrete and movable and give a slightly softer sensation to the fingers than that usually described as 'shotty'.

(*j*) *The skin.* The most striking skin change was undoubtedly the jaundice. The jaundice made its appearance between the third and the sixth day of the fever, generally on the fifth or sixth day, which accounts for the fact that one-half of the icteric cases were admitted between the fifth and seventh days of disease. It rapidly increased in intensity, reaching its deepest and most vivid stage on about the seventh or eighth day, which was the period of maximal severity in most cases and, in those cases in which the sign occurred, corresponded with the time of the 'critical fall' in the temperature. The icterus was essentially a 'yellow' icterus, never greenish or bronzed. In the deeply-coloured cases it has an 'orange', and in the slighter cases a 'lemon' tint, and all gradations of these shades are met with. Fading as a rule was coincident with the subsidence of temperature and fairly rapid; in one or two cases only did it persist in a marked degree during early convalescence. During the first few days of jaundice, while the fever is still high, a flush may be visible beneath the yellow hue, but in convalescence pallor is the rule, though not apparently dependent on any grave anaemia.

Herpes labialis, which may be said invariably to become haemorrhagic, was present on the lips or chin in 43·6 per cent. of the series. The well-known whitish-yellow or brownish vesicles, which are common to other febrile conditions, in this disease become almost immediately changed to brown and later blackened crusts owing to subcuticular haemorrhage. In several cases the herpetic eruption was very extensive, and in one instance it completely surrounded the mouth, invaded the nares, and spread downwards over the chin towards the neck. The black crusts contrasted vividly with the yellow coloration of the facies, and the injected eyes only served to increase the alarmingly morbid aspect of the patient.

Pruritus, presumably due to the jaundice, occurred in three cases, namely, Case 2 (a fatal case), Cases 6 and 34 (both severe cases with recurrence of fever). Case 34, three days later, developed an urticarial rash during a pyrexial recrudescence. A purpuric rash occurred in one case (23). In Cases 10 and 11 '? petechiae' are noted; in several cases numerous small purplish-red spots were found on the trunk which were obviously not petechiae, but suggested much more strongly telangiectases, or minute multiple angiomata. Osler records the occurrence of small spider angiomata in the course of catarrhal jaundice.

(*k*) *The blood.* Varying shades of pallor followed the fading of the jaundice, but never in sufficient degree to suggest profound anaemia. In the cases which recovered, the haemorrhages alone were never extensive enough to have caused a secondary anaemia, nor did the blood-counts during the acute stage suggest any progressive destruction of red cells.

Case 4.		Red cells	6,000,000	Haemoglobin	73 per cent.
Case 6.	5. vi. 16.	„ „	4,400,000	„	88 „ „
	6. vi. 16.	„ „	4,240,000	„	85 „ „
	7. vi. 16.	„ „	5,200,000	„	87 „ „
Case 7.	5. vi. 16.	„ „	8,000,000	„	108 „ „
	6. vi. 16.	„ „	6,640,000	„	105 „ „
	7. vi. 16.	„ „	6,600,000	„	90 „ „
	8. vi. 16.	„ „	5,920,000	„	90 „ „

The definite polycythaemia in Cases 4 and 7 is probably due to the loss of body fluid of which the extreme febrile desiccation of the tissues is an index. The gradual steady return to normal readings both of red cells and the haemoglobin in Case 7 corresponds with the fall of temperature and the general improvement in symptoms.

Serial leucocytic counts and differential counts were not performed.

Experiments relating to the coagulation time and fragility of red cells were reported in the paper by Stokes, Ryle, and Tytler (2).

Section 3. *Prognosis.*

On the experience of this epidemic the immediate prognosis in young men may be said to be very good, in spite of the fact that cases were often so severe as to give rise to that same quality of anxiety as is customarily experienced in a case of lobar pneumonia. Apparently, however, the epidemic must be regarded as mild, for it gave a mortality of only 5·4 per cent. as compared with 10 per cent. in the Greek Hospital at Alexandria (Osler) (8), 20 per cent. in Charville's cases (Trousseau) (7), and 32 per cent. in the Japanese accounts (Inada) (3). It should, however, be taken into consideration that the mild cases were probably recognized in an unusually high proportion in this series, and that observers in previous epidemics do not appear to have recognized or included non-icteric cases. Furthermore, under a military régime there is a much greater probability of recognition of cases than there is in a civil community where many may acquire the disease and remain undiagnosed in their homes. Taking the jaundiced cases only, the mortality in this series becomes 7·5 per cent. Eliminating those cases with jaundice but recorded as 'slight', it becomes 10·7 per cent., which is comparable with the Alexandrian epidemic.

Although they were frequently as severely ill as the graver cases with jaundice the non-icteric cases included no fatalities, and the absence of jaundice may be regarded as a favourable sign. Two of the fatal cases were aged 40 and 53 respectively, and although there is no record of age in the third case, the impression left is that he was certainly not a young soldier. Age and a profound degree of jaundice may be regarded as decidedly adverse factors. Other serious prognostic features are—(i) sustained vomiting, which does not react to treatment; (ii) singultus, which was present in two fatal cases, and in one grave

case with a long relapse which recovered; (iii) haemorrhages from the bowel or macroscopic haematuria; (iv) to a less extent, acetonuria, and albuminuria with casts.

Delirium, tremors, and dyspnoeic attacks indicate a degree of toxaemia which is probably hopeless.

There is no information available to show whether the ultimate prognosis is affected either by the renal or hepatic involvement, or whether there is ever any late lesion of the central nervous system. There were no complications of early convalescence.

TABLE VI. *The Fatal Cases.*

Case.	Age.	Day of Disease on Admission.	Day of Death.	Terminal Symptoms.	Post-Mortem Findings.
2	40	10th	14th	Delirium Dyspnoea Incontinence Muscular twitching Hiccough	Kidneys swollen and congested, with multiple haemorrhages Heart 'mushroom'
9	Not a young soldier	?5th–7th	?7th–9th	Tremors Restlessness	Kidneys swollen and enlarged, with multiple haemorrhages Heart soft
45	53	?6th–7th	?13th	Wandering Haematuria Bowel haemorrhage Hiccough	Kidneys large, with ecchymoses Liver large Haemorrhage in bladder wall

Section 4. *The Fatal Cases and the Cause of Death.*

Table VI summarizes the important features relating to age, time of admission, day of death, terminal symptoms, and P. M. findings in the three fatal cases. The age would appear to be a contributory factor, for the majority of cases were naturally younger men, in whom cardiac and renal efficiency were less likely to be impaired.

The time of admission suggests that the gravity of the disease, in the absence of knowledge obtaining at that time, was not at first recognized in forward-area medical units. Early nursing and symptomatic treatment are important.

The haemorrhages in Case 45 were so small that they could only be regarded as a minor contributory factor, though in a case described in the paper by Stokes, Ryle, and Tytler (2), the haemorrhages seemed to determine the issue.

The actual or determining causes of death which suggest themselves in this series are—(i) The septicaemia. (ii) The jaundice. (iii) An acidosis due to fever, vomiting, and impairment of liver function. (iv) Uraemia due to renal involvement. (v) Heart-failure due to poisoned and degenerate heart-muscle.

(i) That the septicaemia was itself the cause of death seems improbable. The height of the septicaemia is shown to be between the second and fourth days of the disease (see Table V), and the organisms cease to exist in the blood in an active state after the seventh day. The deaths occurred on the fourteenth, ninth (?), and thirteenth (?) days, and the temperature had fallen three and six days before death in two cases. Only in Case 9 does the sudden fall suggest a possible collapse subsidence attributable to the septicaemia.

(ii) Jaundice itself is reputed not to kill, but the impairment of liver function and the decreased efficiency in the digestion of fats may reasonably be held to contribute to the acidosis.

(iii) Acetonuria and in one case (12) the presence of the acetone odour in the breath were evidence of the existing acidosis, or ketosis (see Poulton (11)).

Acidosis may be regarded as a concomitant of all high fevers, especially in children, or when the fever is sustained and the carbohydrate intake limited. It is an indication of the rapid tissue waste due to the fever and the comparative starvation which results (*a*) from the anorexia, (*b*) from the tendency to underfeeding in febrile conditions, (*c*) from such additional factors as vomiting. It is probably associated with the imperfect splitting of body fats.

The writer's attention was drawn to the condition of febrile acidosis during a typhoid epidemic among Belgian civilians in 1915; occasionally it led to such dangerous symptoms as continued vomiting and dyspnoea in patients who had been insufficiently nourished, and it was largely on this experience that he based his principle of insisting on a liberal carbohydrate element in acute febrile conditions (see 'The Value of Sugar in the Treatment of Typhoid Fever', Ryle, *Guy's Hospital Gazette*, Nov. 6, 1915 (13)) and of administering glucose and alkalis in severe cases.

In the three fatal cases the question arises as to whether the dyspnoea and muscular twitchings and delirium in Case 2, the restlessness and tremors in Case 9, and the mental wandering in Case 45 were to be attributed to an acidosis or uraemia, though it should be remembered that acidosis may also be associated with uraemia.

(iv) There was definite evidence of nephritis; in all three cases the kidneys were swollen and ecchymotic. The urine was unfortunately not collected for measurement and urea analysis, but it was almost certainly diminished in amount, though actual suppression did not occur. Perhaps it may be held that acidosis was the cause of the symptoms, and that it was aggravated by the diminished excretion. Dawson and Hume, however, regarded the symptoms as uraemic.

No means were available for conducting estimations of the alveolar CO_2 or otherwise investigating the condition by laboratory methods.

In the closely analogous condition, acute yellow atrophy, the urea output is stated to be greatly diminished, and this is said to be due to the liver-cells failing to manufacture urea from ammonia. In acute yellow atrophy, however, there is often an actual destruction of liver-cells.

(v) In two of the cases at post-mortem the heart was found to be flabby and dilated, and in one of these it was described as resembling the 'mushroom' heart of typhus. Possibly the dyspnoeic attack in this case may have been cardiac in origin rather than due to a central toxaemia, and in both cases myocarditis may well have been the determining cause of death.

Probably, as in other febrile infective diseases, death is due to a summation of factors, which include the general weakness and debility due to the fever and comparative starvation, the acidosis resulting from the same causes, a diminished excretion of toxins due to renal involvement, and—as in typhoid and typhus—a selective toxic action on the heart-muscle.

Section 5. *Therapeutics.*

Specific sera have now been prepared. The writer has seen one case in 1917 which was treated by an intravenous injection of serum, and in which the administration was followed by a dramatic fall in the temperature and a more rapid convalescence than was the usual experience during the 1916 epidemic. Nicolle and Lebailly (10) and the Japanese workers (18) have reported on the use of those sera. Inada reported a disappearance of spirochaetae from the guinea-pig's blood following an injection of salvarsan. Case 4 was given 0·3 gr. salvarsan intravenously on the eighth day, but there was no particular improvement attributable to the injection, and later experience has shown that at that date active organisms would already have ceased to exist in the general circulation.

For lack of specific remedies during the epidemic, treatment was entirely symptomatic. Good nursing was the first essential, attention to comfort and posture in bed and above all to the toilet of the mouth and the herpetic sores being of special importance. The fact that only one case of severe stomatitis occurred in spite of the characteristic xerostoma, and that there were no cases of parotitis, speaks highly for the nursing of these cases. During the acute stages it was with difficulty that the patients were persuaded to take food at all, but an endeavour was made to supply them with sufficient carbohydrate in the form of farinaceous and milk puddings, and a liberal ration of sugar in all their drinks. Fluids were well taken and were unlimited, and when possible oranges and other fruit were provided.

Rectal glucose (1 pint of a 6 per cent. solution once or twice daily) was frequently ordered, partly with a view to increasing the fluid intake and partly to provide an additional quantity of rapidly assimilable carbohydrate.

With the exception of alkalis (sodium bicarbonate) to combat the vomiting and acidosis, drugs were seldom employed. Dover's powder in combination with aspirin was used for the pains, and occasionally morphia had to be given to secure sleep.

Intravenous infusions of normal saline and of sodium bicarbonate (2 per

cent.) in normal saline were given, without apparent benefit in two of the fatal cases.

When the weather was clement patients were nursed in the open air, a procedure which seemed, as in other infective disorders, to exert a very favourable influence on their general condition and progress.

Part III. Discussion and Comparisons.

Section 1. *Variations in Type and Severity of the Disease.*

The cases were roughly classified into slight, moderately severe, severe, very severe, and fatal (see Table III and summary). The slight cases made up 29 per cent., the moderately severe 21·8 per cent., the severe 32·7 per cent., the very severe 10·9 per cent., and the fatal 5·4 per cent. of the total. With the exception of the fact that all the deaths occurred among the jaundiced cases, the icteric and non-icteric types showed but slight differences as regards gravity of symptoms (see summary of Table III). It is probable that a considerable number of slight non-icteric cases escaped diagnosis. The main differences in type, as already shown, are due to the presence or absence of the single symptom jaundice. Neither the other symptoms, such as the haemorrhages, nor the severity—excepting in so far as it was a contributory factor in the fatal cases—seem to have been influenced by the jaundice. Actually the haemorrhagic tendency, as shown by the figures cited, appears greater in the non-icteric cases, though this may be due to the fact that other confirmative evidence was unintentionally more consistently sought and chronicled in cases without jaundice.

One other clinical group is sufficiently distinct to call for a separate classification, and that is the group with respiratory manifestations. Observation of the cases in this group suggested the hypothesis that the spirochaetae sometimes show a selective activity in the pulmonary tissues which they more commonly reserve for the liver, just as in pneumococcal infections the meninges are sometimes selected in preference to the lungs, though both may be affected simultaneously.

Increased respiration rate is shown in 7 (= 46·6 per cent.) of the non-icteric cases, and in 4 (= 10 per cent.) of those with jaundice. Haemoptysis is recorded in 7 (= 46·6 per cent.) of the non-icteric cases, and in 9 (= 22·5 per cent.) of those with jaundice—figures which seem to lend support to the hypothesis.

Section 2. *The Significance of certain Symptoms.*

(*a*) Abdominal pain. At first this was regarded as being either a part of the generalized muscular pain or associated with the constipation and vomiting. Its vagueness and lack of localization favoured this view. On analysis of the

cases, however, it is found to occur in 6 (= 15 per cent.) of the jaundiced cases and in 1 (= 6·6 per cent.) of those without jaundice. Futhermore in this one case and in one of the six with jaundice the liver was enlarged and there was tenderness on palpation; in one also the pain was relieved by lying on the stomach, which suggested that the limitation of the abdominal respiratory movements and of the mobility of the liver was the explanation of the relief so afforded. In other words, in all cases in which abdominal pain was a symptom there was evidence of a hepatitis, a condition which is shown to exist by the histological changes post mortem.

The vagueness and lack of localization of pain were probably dependent on its reference to the whole of the segmental areas involved.

(*b*) Acetonuria. This is recorded in 16·3 per cent. of all cases, in 17·5 per cent. of those with icterus and in 13·3 per cent. of those without. Acetone was also detected in the breath of one case. As has been suggested above its presence may probably be regarded as an index of the rapid and imperfect metabolism associated with high fever; the acidosis, of which it is a sign, is further aggravated by the diminished intake and the vomiting, and possibly by the liver involvement, which may account for its slightly higher recorded incidence in the jaundiced cases.

(*c*) The albuminuria was shown, with the association of red cells, leucocytes, and casts, to indicate the existence of a true nephritis in severe cases, and the swollen ecchymotic kidneys found post mortem confirmed this view. There is no information at present to show whether there is any permanent legacy of damage to renal tissue following the disease, but the general tendency to satisfactory convalescence and the absence of suppression, macroscopic haematuria, or 'smoky' urine, and of oedema suggest that there is a quick return to normal function.

(*d*) Bradycardia and pulse phenomena. The writer had had previous experience of bradycardia in cases convalescent from typhoid fever in 1915, and adduced certain evidences—which admittedly need further support—to show that it was less common in those cases which received a liberal carbohydrate diet during the acute stage of the disease. The theory suggested is that either the actual function or the conductivity of the cardiac muscle-fibres is impaired by carbohydrate starvation at a time when the fever is increasing the rate of tissue-waste. Possibly the muscle glycogen is insufficiently replenished. If the phenomena were due to an actual poisoning of the fibres—a condition which does occur but generally produces grave symptoms—the tendency to recovery would be less marked.

In this series the bradycardia was usually of very brief duration. In the cases with very slow readings, the possibility of heart-block has not been entirely excluded, but it is most improbable, and, as such a transient phenomenon, is not generally recognized. Jaundice is cited as a cause of bradycardia, though Mackenzie (19) states that he has never found it. In this series pulse-rates below 60 were recorded in six icteric and five non-icteric cases,

figures which would give a higher percentage incidence in the absence of jaundice: the lowest pulse-rate—38—occurred in a jaundiced case, but a pulse-rate of 40 is chronicled in another without jaundice; altogether the case for the jaundice as the causative factor of bradycardia in this disease lacks proof, though the writer has seen cases of catarrhal jaundice with little or no fever in which there was pronounced slowing of the pulse.

Marris (17), working at Boulogne, showed that injection of atropin $\frac{1}{50} - \frac{1}{30}$ gr. in fevers other than those belonging to the typhoid group produced a 'release' of the heart, resulting in a greatly increased pulse-rate, and suggested the method as an aid to differential diagnosis in cases of obscure pyrexia. Dawson and Hume (4) report that cases of spirochaetosis ictero-haemorrhagica showed this release. The experiment was only tried in one case of this series, which had been admitted as ? paratyphoid (Case 14). Atropin $\frac{1}{50}$ gr. only raised the rate six beats per minute. However, the blood-culture was negative. On the seventh day the patient developed jaundice, on the eighth day the urine contained albumin, acetone, and casts, and the chart, the pains, and the prostration were all typical of spirochaetosis ictero-haemorrhagica. The guinea-pig was not inoculated until the sixth day of disease and did not become infected.

(*e*) Constipation. Apart from the small intake of food this is believed to be due to the intense dryness which characterizes the disease, and which is so well shown in the mucous membrane of the mouth. There is no meteorism, as in enteric cases, to suggest a paralytic state of the intestinal musculature. The pain and fatigue of straining doubtlessly act as deterrents from the act of defaecation.

(*f*) The fever. This is a close index of the state of the septicaemia. Taking the average maximum temperature recorded in the disease in the series and plotting its occurrence on the different days of disease a curve is obtained which runs parallel to the curve given by the percentage of positive animal inoculations for those days. The marked diurnal remissions, sometimes reaching normal, during the first week, which are shown in some of the cases, probably represent early attempts at immunization, but actual immunization corresponds with the 'critical fall' or the final subsidence, and does not usually occur before the seventh day. The absence of relapse phenomena from the non-icteric cases and their occurrence in one-fifth of those with jaundice suggest that they may synchronize with the liberation of living or dead spirochaetae from the liver. Possibly the milder recrudescences represent a pyrexial reaction due to inactive organisms, and the true relapses are actual re-infections, analogous respectively to the unexplained 'spikes' of temperature and to the genuine relapses of typhoid fever which have been shown to be true secondary blood-infections (Clarke (14)).

The relapse in Case 6 was not accompanied by a return of the jaundice, which continued to fade, though slowly.

(*g*) The haemorrhages. These are in all probability similar to the haemorrhages occurring in other septicaemic conditions, and due to lysis or rupture

of capillary walls. Perhaps the small cutaneous angiomata described above are evidence of injury without rupture to the walls of terminal arterioles.

The haemorrhages do not appear to be attributable to the jaundice. Epistaxis is recorded in 20 per cent. of the non-icteric cases, and 15 per cent. of those with jaundice. Haemoptysis is recorded in 46·6 per cent. of non-icteric cases and 22·5 per cent. of those with jaundice. Haemorrhagic herpes, however, is recorded in a higher percentage (45 per cent.) of jaundiced than of non-icteric cases (40 per cent.).

(*h*) The jaundice. In addition to the post-mortem and histological evidences which showed that no obstruction to the large bile-ducts occurs, and that the obstruction is intra-hepatic and dependent on compression of the small bile canaliculi by leucocytic exudation, clinical evidence suggested at an early date that the jaundice was not due to biliary obstruction in its more commonly accepted sense.

The presence of bile in the vomitus, the absence—though there were exceptions—of markedly fatty stools, the occurrence even of bile-stained faeces, and the failure to discover local signs of gall-bladder involvement, all hinted that the condition was due to other causes.

The red-cell counts and haemoglobin estimations, the absence of haemoglobinuria and of diminished fragility of the corpuscles seemed to negativet he haematogenous theory. It is, perhaps, conceivable that irritation of the liver-cells may conduce to an excessive formation of bile, but whether this occurs or not, there is good evidence both in man and animals that obstruction is the cause of the jaundice, but that it occurs within the liver substance.

Dawson and Hume (4) described a case in which there was much swelling, with plum-coloured staining of the duodenal mucosa, in the neighbourhood of the bile-duct orifice, but in the cases described by Stokes, Ryle, and Tytler (2) the bile-passages and intestines were normal, save in one instance in which there was patchy congestion of the mucosa in the duodenum and below.

The jaundice appears to be an index of the selective localization of the spirochaetae, for though they settle elsewhere, in the lungs and kidneys particularly, the liver would appear to be their favourite site. In this the behaviour of other spirochaetae is followed, for in syphilis, particularly the congenital variety, in relapsing fever, and yellow fever, which Noguchi has recently shown to be a spirochaetal disease, the liver is especially liable to invasion.

(*i*) The rapid respirations. Dawson and Hume state: 'In some cases there is acute bronchitis with respiration-rate up to 30' (4), but although bronchitis was diagnosed in two cases (35 and 42) of this series, in which there was increased rapidity of respiration, the writer is not satisfied that bronchitis was responsible for the symptom. In the first place the bronchitis was slight and with very little expectoration; in the second place rapid respirations were noted in nine cases in which bronchitis was not recorded; in the third place 'grunting expiration' and 'rusty' haemoptysis are not typical bronchitic phenomena, and both suggest far more strongly an interstitial pneumonic condition.

Haemoptysis occurred in six out of eleven cases with rapid respiration. The respiration-rate in six out of eleven cases was 30 per minute or over, and it will be agreed that bronchitis producing a polypnoea of this degree is usually characterized by definite signs and symptoms.

In the guinea-pig pulmonary haemorrhages are a constant feature, and they were present in one human post-mortem (Case 9). The absence of physical signs of consolidation would be readily explained by the small size and scattered distribution of the haemorrhages, though these might be quite sufficient to give rise to pneumonic symptoms.

(*j*) The vomiting. This was formerly regarded as evidence of a gastro-intestinal disturbance or actual infection. Its independence of food, the occurrence during the height of the fever, the usual complete absence of gastro-intestinal inflammatory changes post mortem, and the association with acetonuria, suggested to the writer that it may rather be a symptom of the febrile acidosis akin to the vomiting of feverish children. Generally speaking it was relieved by alkaline draughts and rectal glucose. It does not appear to be associated with the jaundice, for it occurred in 80 per cent. of non-icteric cases, and 75 per cent. of those with icterus. Nor was there anything particularly to suggest that it was central in origin; apart from headache there were never any symptoms to suggest a meningitis or encephalitis.

Section 3. *Comparison of the Disease in Man and the Experimental Animal.*

It is not often that the opportunity is given to the clinician of comparing the symptoms and signs of the same disease occurring in human and animal subjects. Comparative anatomy and pathology have their records and their literature, but comparative symptomatology has not received such close consideration.

In spirochaetosis ictero-haemorrhagica we have a very exact reproduction in the guinea-pig of the human disease. The only essential differences are the greater virulence it possesses for the animal and the consequent early date of death.

The incubation periods—except after passage—fall within comparable limits. The pyrexia precedes the jaundice in both man and animal and the temperature curves are closely similar. The quick rise to a maximum and the sudden drop before death are as characteristic of the disease in the pig as they are in man, but the terminal collapse is even more sudden and dramatic in the former. The duration of the pyrexia is, however, much shorter in the guinea-pig on account of the greater virulence, being 3·5 days (Stokes) on the average as compared with ten days in man. As in man the jaundice becomes deepest towards the time of maximal pyrexia.

The animal's chief symptoms, apart from the jaundice, are an immobility—it sits still in its cage breathing fast—a ruffling of the hair, and refusal to eat.

The immobility and anorexia are probably dependent on the same causes as those which obtain in man.

Section 4. Comparison with Existing Accounts.

The preceding clinical account will be seen to differ from the accounts given in the systems and text-books in a few details only. In these it is generally stated that the spleen is enlarged. In no case in this series could this be confirmed by palpation, and the pathological reports all refer to the spleen as small. Whether the spleen undergoes temporary enlargements sufficient to render it appreciable clinically, or whether its enlargement has been peculiar to certain epidemics, cannot be stated, but it should not be forgotten that until recently the means for differentiating typhoidal jaundice were not generally known, and it is possible that under Weil's disease such conditions became grouped and so gave rise to the statement that splenic enlargement is a feature of the disease. In previous accounts hepatic enlargement also receives undue mention, judging from the experiences of this epidemic, for it only occurred in two out of fifty-five cases in sufficient degree to allow of palpation. In two of the three post-mortem reports the liver is stated to be normal in size and colour, and in the third it is described as large.

The occurrence of non-icteric cases appears to have been mentioned for the first time in the publication of Stokes, Ryle, and Tytler (2). Case 48 is believed to have been the first of these clinically recognized and described; several others in the writer's series received confirmation by animal experiment.

The clinical differentiation of spirochaetosis ictero-haemorrhagica from other forms of febrile, infective jaundice, which is discussed in Part IV below, is a further addition to the picture which has only been made possible by recent experience.

The low mortality and the descriptions of non-icteric cases are the only essential features in which this report differs from recent reports by other observers.

Part IV. The Differential Diagnosis.

Section 1. In the Early Stages and the Non-Icteric Cases.

The fact that patients were admitted with such varying diagnoses as influenza (7, 8); P. U. O.—pyrexia of uncertain origin—(29); ?T. B. (36); pneumonia (16, 53); ?paratyphoid (14); rheumatism (45), while trench fever and ?cerebro-spinal meningitis were also suggested from time to time, indicates not only that the disease itself was unfamiliar, but also that, in its non-icteric types and stages, it resembles many other acute febrile disorders. This is certainly true, and probably only a wide experience of the war-fevers can give

anything approaching confidence in the early clinical differentiation of spirochaetosis ictero-haemorrhagica. The diseases from which its distinction is most desirable, whether from the patient's point of view or for reasons of public hygiene, are—(*a*) The typhoid-group diseases (typhoid and the paratyphoids). (*b*) Cerebro-spinal fever. (*c*) Lobar pneumonia. (*d*) Trench fever.

Haemo-culture, cultures from the faeces and urine, and agglutination tests may settle the problem in regard to (*a*); lumbar puncture may be resorted to for the elimination of (*b*), though in the writer's experience this was never necessary; a high leucocyte count and the bacteriology of the sputum might be necessary to exclude (*c*); and an animal inoculation experiment may determine, though at a late date, the separate nature of the disease from (*a*), (*b*), (*c*), and (*d*).

Apart from these laboratory tests, most of which entail a certain delay, the diagnosis rests, and can usually be arrived at, on clinical evidence alone.

(*a*) The chief features which differentiate spirochaetosis ictero-haemorrhagica 'sine ictero' from cases belonging to the typhoid group are the presence, severity, and persistence of the generalized pains, the vomiting, the albuminuria, and the various haemorrhages. To a less extent the conjunctival injection and the absence of splenic enlargement are of value. If asked to state as briefly as possible the differences between spirochaetosis ictero-haemorrhagica and typhoid or paratyphoid during the first few days of fever, the writer would give it as his experience that spirochaetosis is then already a very definite disease, while typhoid (or paratyphoid) is usually a very indefinite disease. Lacking such stigmata (and they are often absent, especially in inoculated subjects) as splenic enlargement, diarrhoea, and rose-spots, the chief early characteristic of typhoid-group cases may be said to be the absence or vagueness of symptoms. Headache or lassitude accompanying fever are frequently all that is complained of. In spirochaetosis, however, from the moment of its sudden onset, the symptoms are neither absent nor vague, and the pain is the worst symptom. Vomiting and albuminuria are rare in early typhoid-group infections and almost the rule in spirochaetosis.

(*b*) The reasons for confusion between spirochaetosis and cerebro-spinal fever are largely dependent on an insufficient acquaintance with one or both of these diseases. Meningeal forms of spirochaetosis ictero-haemorrhagica have been described, and the spirochaetae are recoverable from the cerebro-spinal fluid (15), but in the writer's experience neither meningitis nor the true symptoms of meningitis occurred. At first sight the severity of the pains, the headache, the fever, the herpes, and the vomiting may well suggest a meningitis, and the presence of Kernig's sign may even be claimed. On a closer inspection, however, the general attitude and decubitus will be found to be very different; the patient may lie on his side and more or less curled up in spirochaetosis, and his stillness is seen to be due to an unwillingness to move rather than to a painful incapacity; he may resent being turned over or handled, but it does not give him the fear and apprehension noticeable in a case of meningitis, and the anxious look of dread is absent from his face. Generally, too, his headache

is a secondary symptom, whereas in a conscious case of meningitis it is invariably the first and worst.

The signs described as Kernig's and neck-rigidity, if properly appreciated, will be found in the sufferer from spirochaetosis to be a pseudo-Kernig's and a pseudo-neck-rigidity, a distinction which holds also in trench fever and other non-meningitic maladies. That is to say, in extending the leg the limitation of movement does not convey to the observer a sense of spasm or of sudden stoppage as from an ankylosis or contracture; rather is it a resistance which can as a rule be gradually overcome, and which is obviously dependent on muscular or fascial pain. The same applies to the neck-rigidity. In meningitis the sensation is that of a steel bar inserted down the spinal canal, and in a bad case one feels that the patient could be lifted as a rigid whole if further force were applied; in spirochaetosis (or severe trench fever) gentle continued pressure overcomes the rigidity, which is dependent on muscular pain and hyperaesthesia and not on actual spasm. The stiffness of a bruised abdominal wall compared with the rigidity of acute peritonitis is an analogous parallel. This distinction between true and false rigidity and true and false Kernig's sign has not, perhaps, received adequate consideration. At times it may be of great value, though where doubt still persists recourse should be had to lumbar puncture.

(*c*) Occasionally the exclusion of pneumonia is a real difficulty. The association of rapid breathing, herpes, 'rusty' haemoptysis, and high fever are so very suggestive, and, though rare, even orthopnoea may be present. The failure to discover signs of consolidation alone cannot exclude pneumonia: again, it is a careful observation of the symptoms which will be most likely to prove helpful. In spirochaetosis the pain is hardly ever referred to the chest, is not acute or 'stabbing', and particularly is not confined to one side of the chest. The general pains outclass the other symptoms, and though the expiratory 'grunt' may be present the breathing is not so distressful as in pneumonia. Excepting in children or with an added pericarditis vomiting is not a frequent concomitant of lobar consolidation, whereas it almost invariably occurs in spirochaetosis. The sputum in spirochaetosis is less profuse, the cough less troublesome. The injected eyes, the prostrate decubitus, the depression or misery rather than anxiety, and the other haemorrhages may all help towards the diagnosis.

(*d*) Trench fever is by far the most difficult fever to differentiate. Between a severe trench fever and a mild or moderate non-icteric spirochaetosis it is wellnigh impossible to draw clear clinical distinctions. In trench fever the limb-pains, backache, headache, conjunctival injection, and even a transient albuminuria may all be present, and, except in the 'spiky' five-day relapsing type, the pyrexia may show a closely similar irregular curve. There is, however, in trench fever a definite tendency for the pains to localize in the shins, the left hypochondrium, or the head; the tongue is often quite clean, or if furred is usually moist; herpes is rare, and haemorrhages, with the exception of epistaxis, are not recorded, though the writer is of the opinion that transient haematuria

with frequency occasionally occurs; vomiting is very rare; the spleen is frequently palpable. In the later stages of the campaign—possibly owing to re-infections or the chronicity of infections—enlargement of the spleen became very much more common in trench fever; the enlargement is of a definite type, giving the sensation of a hard, almost sharp edge, and never that of the soft typhoid spleen; it is seldom felt lower than two fingers' breadths below the costal margin on inspiration.

Familiarity with the varieties of trench fever charts may also assist in the diagnosis.

Five cases at first considered to be spirochaetosis ictero-haemorrhagica were excluded from this series as trench fever; one was excluded as lobar pneumonia; and one, although he gave a history of pains, vomiting, and epistaxis, and came from the same unit as a jaundiced case with a 'positive pig', had to be excluded, as *B. paratyphosus B* was cultivated from his blood.

Section 2. In the Icteric Cases.

The differentiation in the cases with jaundice is, generally speaking, not so difficult, since the high fever alone, especially in the absence of other febrile epidemics, limits the field. The chief possibilities are typhoidal and paratyphoidal jaundice and 'catarrhal jaundice'. Catarrhal jaundice was not a common malady at the time of the epidemic, nor at other times on this particular front in the course of the writer's experience. Two cases, which had at first been regarded as spirochaetal but were later excluded from the series, are described below by way of contrast.

(i) L/Cpl. S. Admitted eighth day of disease. Started with vomiting, and jaundice was noted on the same day. Apart from vague abdominal pains the patient had had no symptoms, but said he felt feverish at night for the first four days, during which time he was in the trenches. No limb-pains, eye-pains, haemorrhages. Jaundice fairly deep; eyes a little injected but not sore. Liver margin palpable in epigastrium 2 inches down, and not tender. No glands enlarged. No fever on admission.

(ii) Pte. B. Admitted with one week's history of gastric disturbance and headache. Liver slightly enlarged. No limb-pains, prostration, herpes, or haemorrhages. The patient very cheerful. Pulse 40–48. Came in as a walking case.

The mental outlook, the absence of definite symptoms, and the admission of one of them as a walking case are in themselves distinctive evidence.

The jaundice of typhoid and paratyphoid more commonly follows the febrile stage, but Murray Leslie (16) has described two cases in which jaundice preceded the fever. In a case seen by the writer in 1915 the jaundice appeared suddenly in association with biliary colic and a slow pulse late in convalescence from typhoid fever.

The jaundice associated with other fevers and septicaemic states is not likely to give rise to difficulties, though the jaundice associated with relapsing

fever and with pneumonia (Osler (8)) might well present closely similar pictures. From acute and chronic forms of obstructive jaundice there should be ample distinctions.

In the later phases of the grave cases, and especially of those which have a fatal issue after an apyrexial period, the similarity to icterus gravis or acute yellow atrophy must be so close, that, lacking a clear history or other co-incident cases, a clinical differentiation would be almost im possible.

Leucin and tyrosin were sought in the urine of one case of this series but not found, and diminution of the liver volume was never suspected; but on such differences alone an opinion could not be formed, and, as Trousseau has pointed out, alterations in the size and structure of the liver are by no means constant in icterus gravis. It is possible that a certain proportion of cases recorded as icterus gravis have been cases of spirochaetosis ictero-haemorrhagica. Except in its greater severity and the tendency to gastric haemorrhage yellow fever is clinically the same disease as spirochaetosis.[2]

Section 3. *Conclusion.*

A detailed tabular and statistical description of a disease must always be less graphic and picturesque than a brief pen-picture of a few striking cases. While fully conscious of this the writer has adhered to his original intention of providing a complete, rather than a pictorial, presentation of this disease and its variations, based upon his own observations of a consecutive series.

Spirochaetosis ictero-haemorrhagica had already been subjected to such thorough research at the hands of the pathologists that in its clinical aspects alone did it seem to ask completion.

It is this task of completion, together with a co-ordination of bedside and laboratory findings, that the writer has endeavoured to fulfil.

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[2] At the time of writing Noguchi's discovery of the spirochaeta of yellow fever was not announced. Except in mode of transmission the two diseases would now seem to be almost identical; indeed, it may even be that yellow fever was originally merely spirochaetosis ictero-haemorrhagica passed by *Stegomyia* from rodent to man.

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AN INVESTIGATION INTO THE METABOLISM IN INFANTILE ATROPHY, WITH SPECIAL REFERENCE TO THE RESPIRATORY EXCHANGE[1]

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Introduction.

THE present investigation has been undertaken in the endeavour to determine whether in infantile atrophy, as ordinarily understood, there is an error in metabolism which will explain the inability of infants suffering from this condition to develop at the normal rate.

It has been shown that in infantile atrophy protein (4) (14) absorption from the bowel (except when there is diarrhoea) and nitrogen excretion in the urine are practically normal, and failure to thrive cannot therefore be attributed to faulty protein metabolism. Recently Hutchison (7) has shown that fat digestion and absorption in the atrophic child is practically as efficient as in the normal; hence, if fat be to blame, it must be the metabolism of fat within the organism rather than its defective digestion and absorption which is responsible for the wasting.

It is also possible that there may be some defect in the carbohydrate metabolism. The carbohydrate may either be badly absorbed from the intestine or it may not be properly used in the tissues either as a fuel or as a source of body fat.

It seemed that by investigating the respiratory exchange in infantile atrophy some light might be thrown on the problem. By this means the nature of the metabolism can be determined; for not only can the quantity of material metabolized be estimated, but the nature of this material, whether carbohydrate or fat, can be ascertained.

A considerable amount of work has already been done on the respiratory exchange in infancy, chiefly by Benedict and Talbot (1), who give an excellent review of the literature. It is quite clear that it is not easy to determine the basal metabolism in infancy, since not only is it most difficult to get uniform

[1] This investigation was carried out under the auspices of the Child Life Investigation Committee of the Medical Research Council, by whom the expenses were defrayed.

conditions of muscular repose, but also the size of the child and the proportion of fat and other metabolically inactive tissue in its body vary between very wide limits.

It is generally admitted that the basal metabolism is directly dependent on the amount of muscular tissue in the body, but I have not been able to find any method of gauging this. Until some method has been devised one has to fall back on such measurements as body weight, body surface, length, and age. Benedict and Talbot (2) found in very young infants (under three weeks) that a constant figure was obtained if the heat output per square metre of body surface (Lissauer) were divided by the body length, and by this means they devised a formula for estimating the body surface which is probably more accurate than any other, but unfortunately this formula is not satisfactory when applied to older children. Benedict and Talbot were dealing with practically new-born infants, and probably the configuration and state of nutrition of their subjects were fairly constant; but if this formula be applied to the older children whom they investigated it is found that there is a very wide variation, a divergence which I found to apply to my cases. It seems clear, therefore, that at present no practical method of measuring the surface area of infants satisfactorily has yet been found, and anything more than a very approximate estimate of the normal basal metabolism has still to be determined.

The Method employed in determining the Respiratory Exchange.

The apparatus used was essentially the same as that employed by Benedict and Talbot in their work on the respiratory exchange in infants. It consisted of a copper box surrounded by a water jacket with a lid hermetically sealed by having its down-turned edges submerged in the water of the water jacket. A large pane of glass was let into the lid for observation purposes. Within the box a special crib was arranged. One end of the crib rested on a knife-edge, and the other was slung by a spring attached to a projecting arm. Under the end supported by the spring a Politzer bag was placed and connected by rubber tubing to a narrow pipe leading through the double walls of the box to the exterior. This was attached by rubber tubing to a delicate tambour, and in this way the movements of a child in the box were registered on a slowly moving drum.

The various degrees of activity were divided into six classes. When the child made very few movements during a period this was classified as I; the child was usually asleep during the whole of such a period. When there were more movements, but when the child was on the whole very quiet, Class II was assigned to such an experiment. Class III indicated considerable movements, and the subsequent classes were arranged so that when the child was active practically the whole time the activity was classified as VI. Fig. 1 is a typical tracing showing activity I.

At the end of the box farthest from the exit pipe a thermometer graduated

to 0·1 of a degree centigrade was inserted through the wall of the box midway between the top and the bottom.

A spirometer, by means of which the pressure within the apparatus was kept equal to the atmospheric pressure, was connected by means of a ½-inch pipe with the interior of the box. The bell of the spirometer was made of very thin copper and was counterpoised by a weight slung on pulleys. A pointer was attached to the counter-weight, and by this means the height of the spirometer bell could be recorded on a vertically placed millimetre scale. It was found that the spirometer was so extremely sensitive to changes in volume of the air in the apparatus that by its movements the pressure within the box was maintained constantly at atmospheric pressure (as shown by a delicate oil manometer), except during the brief periods in which oxygen was being let into the apparatus and the spirometer bell was rising. This was of the greatest impor-

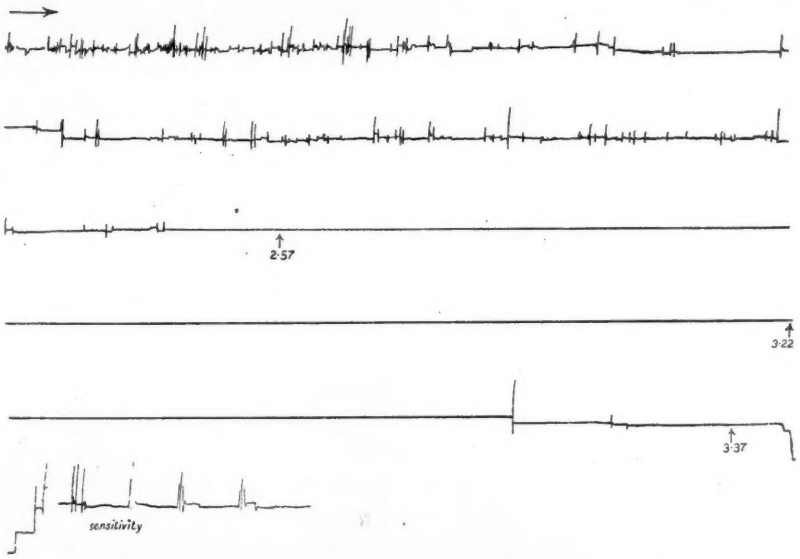

FIG. 1. The experiment began at 2.57 and ended at 3.37. Activity I.

tance in estimating the quantity of oxygen used, for by arranging the supply of oxygen so that the height of the spirometer bell was at the same level at the end as it was at the beginning of an experiment the volume and pressure of the air within the apparatus was the same at the start and finish of an experiment, changes in temperature being the only correction that was necessary.

A ½-inch tube led from the box to the psychrometer, which consisted of a wet and dry bulb thermometer arranged so that the air passed over these immediately on leaving the box. The psychrometer was connected by ½-inch tubing to the Benedict universal apparatus, which was provided with double absorbers.

The oxygen was supplied from a cylinder and passed through a Bohr meter immersed in a water-bath, but before passing through the meter it was bubbled

through water in a wash bottle also immersed in the water bath. From the meter it was delivered by rubber tubing to the apparatus. The meter was calibrated by weighing a small cylinder before and after passing oxygen through it, and comparing the weight of oxygen lost with the quantity registered by the meter. The oxygen contained on the average 2 per cent. impurities: allowance was made for this.

Each day before use the apparatus was tested for leaks.

The Method of carrying out an Experiment.

All the experiments were done between 2.15 p.m. and 4.30 p.m. The child, wrapped in a blanket, but with its arms free, was placed on a thick folded blanket in the crib, its head resting on a pillow, and there can be no doubt that the children were quite as comfortable as in their ordinary cots. The apparatus for registering the movements was adjusted, the lid closed, and the pump started. The spirometer bell was lowered so that the indicator was about half-way up the scale and the preliminary period was commenced. While this was proceeding a pair of soda-lime and sulphuric acid bottles, carefully weighed, were connected up to the apparatus in readiness for the next period. The necessary barometric and temperature readings were taken, and a fairly free supply of oxygen let into the apparatus. The preliminary period lasted about 30 minutes, or sometimes longer if the child was restless. Before starting a period from which the respiratory exchange was to be determined the meter was read and the temperature at either end of the box recorded. The current of air was then diverted through the weighed absorbers and the position of the pointer on the counterpoise of the spirometer read on the millimetre scale. Naturally as CO_2 was absorbed the bell of the spirometer gradually sank, and oxygen was added as required. Two minutes before the end of such a period the temperature at each end of the box was again recorded and oxygen added in order to bring the bell of the spirometer to a slightly higher level than that at which it started. As it gradually sank the pointer on the counter weight was carefully watched, and whenever it reached the point at which it started at the beginning of the period, the air current was diverted to the other set of absorbers and the experiment was at an end. The meter was then read and the CO_2 absorbers weighed. At the end of each experiment, but before the child was removed from the crib, the sensitivity of the movement recorder was tested by dropping a 50-grm. weight from the height of four inches on to the pillow on which the child's head was resting.

The mean temperature of the air in the apparatus varied in different experiments from 15° C. to 21° C. The usual temperature was about 18° C. During an experiment there was usually a rise in the temperature of about 0·2° C. This was invariably taken into consideration in estimating the amount of oxygen used. The following is an example of a typical experiment:

Weight of CO_2 absorbed	3·41 grm.	Meter readings of oxygen	2·14 litre
Volume	1·77 litre	Corrected for temperature pressure and impurities	1·90 litre
		Increase in volume of air in apparatus due to rise in temperature	0·13
		Total O_2 used	2·03 litre

Temperature of Apparatus.

	Thermometer 1.	Thermometer 2.		
beginning	18·4°	16·6°	Temperature of water bath	15·2
end	18·6°	16·9°		
Barometer	745 m.m. Hg.		Temperature of barometer	16·4°
Mean end temperature of apparatus				17·7°
Increase in temperature				0·25°
Time 3.03 p.m. to 3.43 p.m.				
Respiratory quotient				0·87

Control Experiments with Alcohol.

About every fortnight, or sometimes more frequently, the $CO_2 : O_2$ quotient for the combustion of absolute alcohol was determined. This was done by placing a small spirit lamp in the box and estimating the quantity of CO_2 given off and the quantity of O_2 utilized during a period of about 30 minutes. The experiments were carried out in precisely the same way as those with children. The quotient for alcohol is 0·66. In these experiments the quotients varied between 0·62 and 0·70, the average being 0·65 (Table I).

TABLE I.

Date.	$CO_2 : O_2$ quotient.	Date.	$CO_2 : O_2$ quotient.
21.10.19	0·67	10.2.20	0·68
16.11.19	0·68	24.2.20	0·63
23.11.19	0·65	15.3.20	0·68
30.11.19	0·63	29.3.20	0·70
14.12.19	0·62	30.4.20	0·67
11.1.20	0·66	18.5.20	0·63
25.1.20	0·66	21.5.20	0·68
	Average 0·65		

The Respiratory Exchange in Children.

All the children were patients in the Royal Hospital for Sick Children, Glasgow. Their ages varied from three weeks to two years (only two were more than a year old). They were all under weight, but eleven were within 25 per cent. of their expected weight. In all the cases, except in a few specified instances, the temperature was normal or slightly subnormal, and as far as possible only children in whom there was no gross gastro-intestinal disturbance or other obvious disease were examined.

The majority of the cases were fed on whole milk with the addition of variable amounts of carbohydrate in quantities suitable for the age.

TABLE II.

Subject.	Litres oxygen per hour.	Litres CO_2 per hour.	Respiratory quotient.	Activity.	Body weight in kilos.	Length in centimetres.	Time in minutes after food that experiment began.	Total calories per 24 hours calculated from O_2.	Age in months.
McG.	3·09	2·73	0·88	II	3·53	57	47	363	6·0
,,	3·135	2·95	0·94	I	3·51	57	70	374	6·0
,,	3·34	2·63	0·78	I	4·02	58	66	381	7·0
,,	3·63	2·99	0·82	II	4·11	58	40	420	7·5
,,	3·95	3·14	0·77	I	4·90	61·5	67	452	9·0
,,	3·42	3·09	0·90	I	5·5	62·2	152	404	9·75
Be.	2·77	2·52	0·90	III	2·94	54	49	312	4·25
,,	1·99	1·68	0·84	II	2·97	54	54	230	4·25
,,	2·39	1·71	0·71	III	3·00	54	65	269	4·5
,,	1·82	1·53	0·84	I	3·08	54	54	211	4·5
,,	2·16	1·77	0·82	II	3·09	54	73	250	5·5
,,	2·13	1·79	0·84	I	3·06	54	128	258	6·0
,,	2·43	2·05	0·84	I	3·57	54·5	60	282	6·75
,,	2·67	2·64	0·98	IV	3·8	55	65	322	7·25
,,	3·27	3·37	1·03	III	4·13	57	64	396	7·5
,,	2·91	2·72	0·93	I	4·13	57	60	347	7·5
,,	3·3	2·56	0·77	II	4·4	57	94	377	7·75
,,	3·46	3·18	0·91	I	4·87	58	150	410	8·5
Wt.	3·24	2·93	0·90	II	4·13	61	47	381	7·0
,,	3·16	2·98	0·94	I	4·13	61	45	376	7·0
,,	3·45	3·62	1·05	II	5·24	62·4	101	418	9·0
Gn.	3·92	3·17	0·80	II	5·66	68·1	70	451	6·0
Mm.	3·44	2·92	0·84	I	8·15	72·5	84	400	13
Hr.	2·52	2·39	0·96	III	4·30	52·2	52	302	3
,,	2·51	2·18	0·87	I	4·26	52·2	45	288	3
Sn.	2·31	2·02	0·87	I	3·48	54	58	171	3
McL.	2·52	2·31	0·91	II	4·11	57	71	297	3
,,	2·77	2·30	0·82	III	4·25	57·5	60	320	3·25
,,	3·19	3·21	1·0	II	4·36	60·2	79	386	5
,,	3·67	3·19	0·86	II	4·67	60·2	160	429	5·5
,,	3·48	2·92	0·83	II	4·84	61·5	71	404	6
Mk.	4·68	4·67	0·99	II	8·97	69	45	564	12
Cn.	2·30	1·99	0·85	I	3·05	55·1	65	269	6
,,	2·21	1·68	0·76	I	3·14	55·1	78	246	6·25
,, *	2·88	2·51	0·87	I	3·45	58	54	338	6·75
An.	3·03	2·79	0·92	I	3·74	58·5	60	360	7·75
Ry.	2·34	1·97	0·83	II	4·08	55	80	272	2·25
,,	2·85	2·19	0·76	I	3·85	60·5	68	325	5·75
,,	2·34	1·98	0·84	I	4·16	60·5	62	272	6·0
,,	3·20	2·98	0·93	I	4·84	61·5	69	381	7·0
,,	3·48	3·18	0·91	II	5·1	61·5	72	412	7·25
,,	3·04	2·66	0·87	II	5·30	61·5	63	356	7·75
Mn.	3·01	2·52	0·83	IV	4·19	65	52	349	24
Ls.	2·47	2·04	0·82	II	3·77	56·3	60	288	4·0
,,	2·52	1·98	0·78	I	3·74	56·8	61	288	4·5
,,	2·23	2·06	0·92	I	3·77	56·9	60	264	5·0
,,	3·00	2·56	0·85	I	4·05	57	63	349	6·0
,,	2·53	2·43	0·95	I	4·0	57·4	68	303	6·25
,,	2·50	2·00	0·80	I	4·11	57·5	54	288	6·5
,, †	4·14	3·31	0·79	I	4·42	59·5	58	476	7·5
,,	3·26	2·97	0·91	I	4·33	59·5	65	386	7·5
Dn.	3·82	3·52	0·92	I	8·25	72	67	453	9
,,	4·24	3·79	0·89	III	8·27	72	72	500	9
,, ‡	4·65	4·35	0·93	II	8·33	72·4	51	552	9·25

* Temperature at end of experiment 99·2° F.
† ,, ,, ,, 99·6° F.
‡ ,, ,, ,, 99·0° F. (Developing measles.)

TABLE II (*continued*).

Subject.	Litres oxygen per hour.	Litres CO_2 per hour.	Respiratory quotient.	Activity.	Body weight in kilo.	Length in centimetres.	Time in minutes after food that experiment began.	Total calories per 24 hours calculated from O_2.	Age in months.
Me.	1·95	1·69	0·87	II	2·80	51·5	52	228	1·75
„	2·28	2·07	0·90	II	3·37	53	62	269	2·25
„	2·26	2·14	0·94	I	3·65	55	81	270	2·75
„	2·49	2·21	0·88	I	3·82	56	63	293	3·0
Lh.	2·64	2·29	0·86	III	4·0	53·5	60	308	2·25
„	2·17	2·05	0·94	I	4·08	53·5	68	253	2·25
A. W.*	1·22	1·06	0·86	I	2·32	50·5	40	143	−0·25 0·75
„	1·62	1·22	0·75	I	2·78	50·5	50	184	0·0 1·0
Cl.	3·45	3·07	0·89	I	5·0	62·3	81	406	5·75
„	3·22	2·94	0·91	IV	5·01	62·3	77	381	6·0
Br.	3·92	3·54	0·90	III	6·01	65·6	65	463	7·0
„	4·23	3·72	0·88	III	6·0	65·6	76	497	7·0
Pr.	1·98	1·80	0·90	I	3·31	53·8	60	234	3·0
„	2·48	2·40	0·96	IV	3·82	54	85	298	3·75
Le.	2·03	2·02	0·97	III	3·6	53	91	246	3·25
„	2·46	2·0	0·81	I	3·71	55	45	284	3·5
McV.	2·62	2·19	0·83	II	3·46	54·7	70	304	3·0
„	2·97	2·59	0·87	V	3·51	54·7	72	348	3·25
„	2·58	2·45	0·94	III	3·57	54·7	60	308	3·25
Hn.	3·09	2·43	0·79	IV	6·8	71	53	355	6·5
De.	3·33	3·09	0·92	V	4·3	59·5	86	395	8·5
Stn.	2·56	1·88	0·73	I	3·74	60·2	93	290	4·25
McN.	2·16	2·10	0·97	I	3·37	59	62	260	4·75
Fy.	2·95	2·64	0·89	I	4·65	57·5	65	348	6·75
Gon.	2·54	2·25	0·88	IV	3·94	58	44	298	2·0
„	2·58	2·35	0·91	I	4·16	59	48	305	2·75
McD.	2·76	2·46	0·89	I	3·8	56	57	325	5·75
An.†	2·16	2·07	0·96	II	2·75	52	69	259	3·5 1·5
„	2·60	2·45	0·94	II	3·03	53·5	74	310	3·75 1·75
Pm.	2·53	2·13	0·84	II	3·74	58	126	294	4·25
We.	2·81	2·55	0·90	IV	4·16	58·5	109	332	3·25
„	2·71	2·40	0·88	II	4·11	58·5	53	319	3·25

* This child was one month premature.
† „ „ „ two months premature.

The experiments were all carried out 45 to 160 minutes after food had been taken (the great majority were within 90 minutes of the feed), and probably in every case absorption was at its height. This, of course, meant that the stimulating action of the food was in full play, and the period was chosen as it was considered important to obtain muscular repose as far as possible. It is obviously much easier to obtain this in a child recently fed than in one that is anxiously awaiting its next bottle, while, on the other hand, to carry out a series of fasting experiments would have entailed the estimation of varying degrees of muscular activity, a much more imponderable factor than the estimation of the food taken.

In Table II the full data on which the following discussion is based are given. Absolute accuracy is not claimed; probably the very high and very low respiratory quotients are not correct; but the vast majority of experiments are well

within the realm of possibility, and the error is probably no greater than the error observed in the alcohol experiments.

Discussion of Results.

The respiratory quotients. For reasons that will appear later the cases examined were divided into two classes, namely those whose weights [2] were greater than 65 per cent. of the expected weight for the age, and those whose weight was less than 65 per cent. of the expected weight. In the former class the average R. Q. was 0·88, in the latter 0·87. Had the markedly atrophic subjects been unable to utilize fat we would have expected that their respiratory quotients

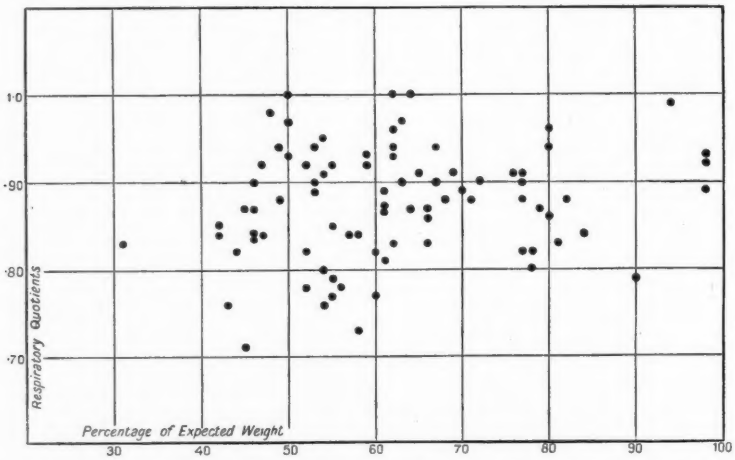

CHART I. Records of 84 observations on 33 infants showing the percentages that the observed weights of the subjects were of the expected weights and the respiratory quotients.

would have been higher, while if carbohydrates were not being utilized very low respiratory quotients would have been found. These figures do not lend any support to either of these suggestions. In Chart I the respiratory quotients and the percentage the weights of the subjects were below the expected weights are shown, and it is clear from this that there is no obvious relationship between the R. Q. and the state of nutrition.

The Heat Production. This was calculated from the R. Q. and the oxygen intake. It is generally admitted that this method of estimating heat production (indirect calorimity) is almost as accurate as the direct method (6, 10). Only cases showing an activity of I or II are considered under this heading.

Speaking broadly, the total heat production varied according to the size of

[2] Throughout this investigation the expected weight has been taken to be the average weight for age as given in Holt's (4) tables. Probably a more accurate estimate would have been made by taking into consideration the weight at birth, but unfortunately it was hardly ever possible to obtain an accurate record of this.

the infant. The heat production per kilo of body weight showed wide variations, but it is clear from Chart II that the greater the degree of emaciation the higher is the heat output per unit of weight.

Since the heat output is dependent on the amount of active metabolic tissue, this would indicate that in atrophic children the loss of weight is apparently largely at the expense of fats or other metabolically inactive tissues.

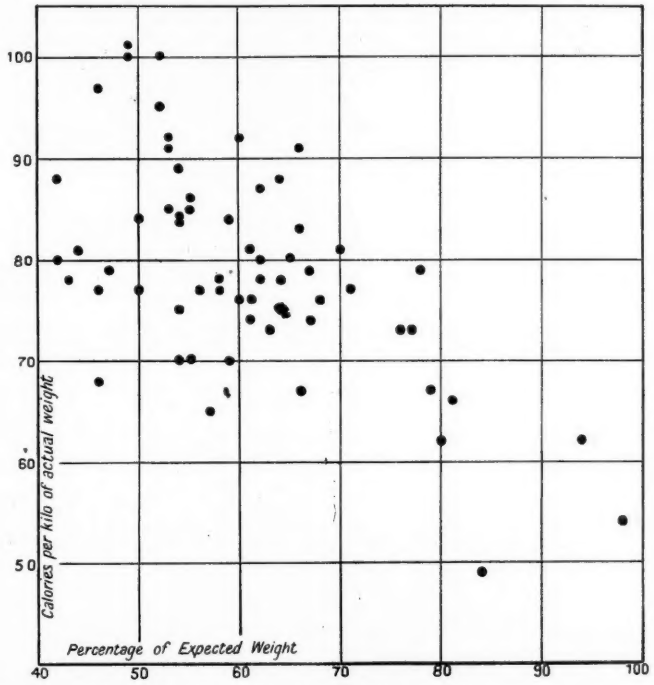

CHART II. Showing heat output per kilo of actual weight and the percentages that the observed weights of the subjects were of the expected weights.

It is well known that in starvation the body first calls up all available stores of carbohydrate, and when this has been utilized, fat and protein are used by the organism. The amount of protein used is roughly in inverse ratio to the quantity of fat stored in the body at the beginning of the fast (8). In partial starvation, when a sufficiency of protein is given in the food, the loss of weight takes place largely at the expense of fat, the loss of protein is small, and there may even be a retention of nitrogen (15).

The atrophic infant may be considered to be in a state of partial starvation. The protein intake is probably sufficient for its needs (12), but there is a deficiency (whether the cause be faulty absorption or defective utilization) of carbohydrates or fats. In this case a stage will be reached in which the muscle protein will be called upon to supply the energy necessary for life, and whenever this commences muscle will cease to grow, and as atrophy advances there will be actual loss of

muscular tissue. During the early stages of atrophy, before the active metabolic tissue is encroached upon, the heat output should not be altered, but whenever muscular wasting or even arrest of growth sets in the heat output should be lower than the normal for the age of the subject.

If a diagram be constructed showing the calories utilized per kilo of expected weight and the percentage that the subject is below expected weight, then we should find that when the weight reaches a certain point below the expected weight the caloric output per kilo of expected weight should decrease; above this point, that is, when there has only been wastage of fats, the caloric output per kilo of expected weight should be approximately constant.

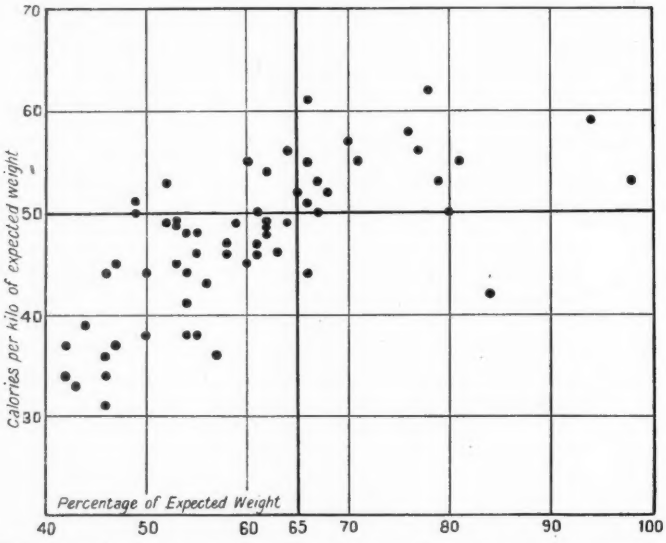

CHART III. Showing heat output per kilo of expected weight and the percentages that the observed weights of the subjects were of the expected weights.

In Chart III such a diagram has been made from the figures obtained from all cases examined with an activity of less than III and with normal temperatures. It will be seen from this that, as expected, the cases under a certain percentage of expected weight show a caloric output which gradually diminishes as they become more and more atrophic, while cases above this point all show a fairly constant heat output. This point is 65 per cent. of the expected weight. Above this the heat output is fairly constant, between 50 and 60 calories per kilo of expected weight; below this it gradually diminishes. It seems justifiable to draw the conclusion from this that until 35 per cent. of the weight has been lost there is no loss of active metabolic tissue. The true figure is probably somewhat higher than this, for, owing to loss of fat, the insulation of the body is not efficient, and consequently the temperature of the body is only maintained by an increased metabolism (chemical regulation of temperature).

Availing myself of the data given by Benedict and Talbot (1) in their paper

dealing with children of approximately the same age as mine, I have constructed a similar chart, and this shows an almost identical state of affairs (Chart IV). At 65 per cent. of expected weight the heat output falls below 47 calories per kilo of expected weight, and gradually diminishes as atrophy advances. Above 65 per cent. it remains fairly constant between 47 and 60 calories per kilo of expected weight. The closeness of these figures to those obtained by me is striking. The fact that their caloric output is slightly lower than mine is probably explained by the fact that many of their observations were made when food had not been taken for over three hours.

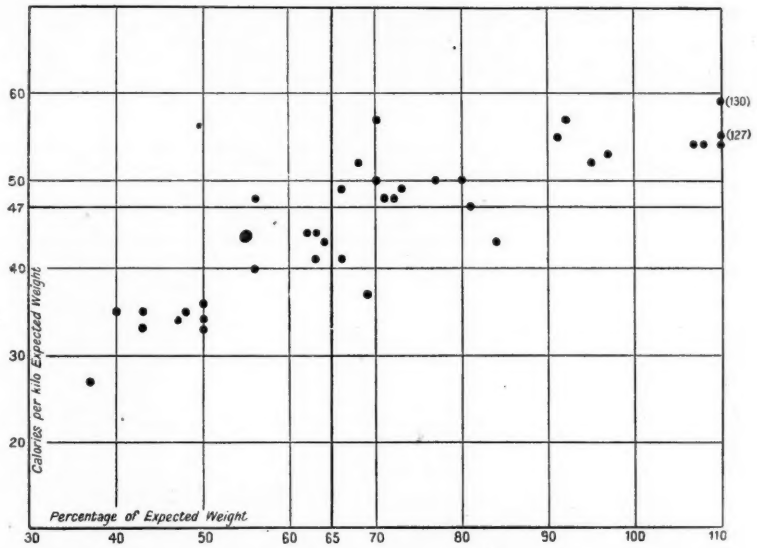

CHART IV. Showing heat output per kilo of expected weight and the percentages that the observed weights of the subjects were of the expected weights. Benedict and Talbot's cases.

If the above observations are sound they are of considerable importance in the study of infant metabolism, especially in its application to abnormal children. For by this means we are able to fix a standard heat output for any age (within the limits of age investigated so far), and if the child shows a metabolism above or below this standard we must look for some abnormality. An example of this is given in the case of baby Dn., who was a normal child, aged nine months, weighing only 2 per cent. less than its expected weight. On the 12th of Feb. 1920 its heat output for 24 hours was found to be normal (53 calories per kilo expected weight). On the 17th of Feb. 1920 its heat output had increased to 65 calories per kilo of expected weight, and its temperature immediately after the experiment was found to be 99° F. Next day the temperature was 101° F. Koplick's spots were present, and it was transferred to a fever hospital, where it passed through a typical attack of measles. In this case the increase in the metabolism above the normal standard found five days previously was, no doubt, due to the attack

of measles which was developing. Moreover, this method of fixing a standard metabolism tends to confirm the commonly accepted idea that the food requirements of an infant should be regulated by age rather than by weight (13). Children who are not less than 35 per cent. under expected weight have a heat output as great as normal children, and consequently require a diet of as great caloric value as normal. Those who are more than 35 per cent. below expected weight require an amount of nourishment somewhat less than normal, but none the less considerably more than indicated by their actual weight. The relative quantity of nourishment in these cases should gradually diminish as the difference between observed weight and expected weight increases. Conversely, as shown by Benedict and Talbot's cases (Chart IV), a child that is over weight should receive the quantity of food suitable to its age rather than the quantity that its weight would suggest.

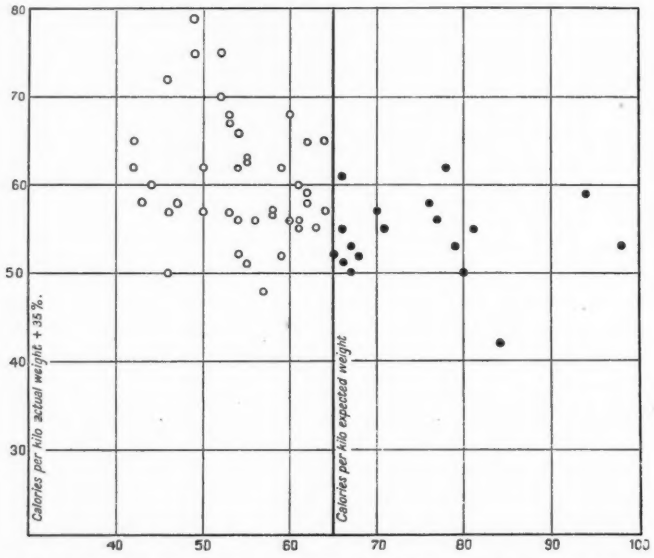

CHART V. Showing percentage of expected weight, and (1) heat output per kilo of actual weight plus 35 per cent. in subjects less than 65 per cent. of expected weight; (2) heat output per kilo of expected weight in subjects more than 65 per cent. of expected weight.

The foregoing observations do not yield much information regarding the error in metabolism associated with atrophy. The respiratory quotients give no definite indication of the inability of the organism to burn either fat or carbohydrate. If the infants were unable to burn the former the R. Q. would tend to be high, while if the latter could not be utilized (as in diabetes) there would be glycosuria and a low R. Q. It is generally recognized that infants put on weight on a diet rich in carbohydrate more readily than on any other. If, for any reason, there is inability to convert carbohydrate into fat, the excess carbohydrate above the direct needs of the organism will have either to be excreted, stored as glycogen, or burned. But glycosuria is uncommon (it was not observed in any of

my cases), and there is no evidence of excessive storage of glycogen, so we are left with the only other alternative that it is excreted as CO_2 and water, that is burned. If this is the case we should expect to find an excessive heat output as long as there is carbohydrate available. At first sight this seems to be the case (Chart II), but it must be remembered that the children below 65 per cent. of their expected weight had lost most of their fat, and consequently their heat output appears high when compared to that of the better nourished children. Supposing we take the subjects who were more than 35 per cent. below their expected weight and add to their observed weight 35 per cent., that is to say, add on the fat that they should have had, and with this figure, i.e. observed weight plus 35 per cent., find their heat output per kilo. Then if they are utilizing carbohydrates extravagantly their heat output should be high when compared to the heat output per kilo of expected weight of the children who had lost less than 35 per cent. of their expected weight. This comparison has been made and is shown in Chart V. It is evident from this that the markedly atrophic children had on the whole a greater heat output than those who were less than 35 per cent. below expected weight. The variations in heat output are wide, but it affords some evidence to show that in atrophy the metabolism is carried on less economically than in health.

TABLE III.

Name.	Weight.	Expected weight.	Age in weeks.	% of expected weight.	Quantity glucose. grm.	Glycosuria.
An.	2·72	6·00	14	45	9	0
Pr.	3·28	5·60	12	59	10	Trace
McN.	3·4	6·7	19	50	10	0
McV.	3·48	5·44	11	64	8	0
,,	3·47	5·44	11	64	11	Trace
Pm.	3·62	6·25	16	57	15	0
,,	3·67	6·4	17	57	20	0
Le.	3·63	5·75	13	63	7	0
,,	3·7	6·00	14	61	11	0
McD.	3·8	7·7	27	49	15	0
,,	4·1	7·81	28	52	17	0
Ls.	4·08	7·91	30	51	9	0
,,	4·33	8·1	32	53	8	0
,,	4·45	8·1	32	55	15	0
We.	4·13	5·75	13	72	15	0
McG.	4·22	7·81	29	54	15	0
Se.	4·25	7·35	25	57	12	0
,,	4·36	7·5	26	58	18	0
,,	4·36	7·5	26	58	25	0
,,	4·5	7·5	26	60	30	0
Je.	4·33	7·5	26	57	11	0
De.	4·42	8·5	37	52	11	0
,,	4·42	8·5	37	52	14	0
Hs.	4·87	9·0	41	54	12	0
Cl.	5·00	7·35	25	68	12	0

Carbohydrate Tolerance. There are two other possibilities to account for the failure of these infants to thrive. Either some of the carbohydrate is excreted in the urine or it is not absorbed. In order to test the first of these hypotheses I have examined the tolerance for glucose in fifteen cases (Table III). All the

subjects were more or less under weight, and only patients in whom there was no actual gastro-intestinal disturbance at the time of the experiment were examined. In every case the infants were being fed on whole milk or some modification of this. They were fed at four-hourly intervals, except between 10 p.m. and 6 a.m., when there was an interval of eight hours. The test was carried out by substituting a solution of glucose for the 6 a.m. feed, so that when the experiment began they had been fasting for eight hours. Before the glucose was given the infants were placed on a metabolism bed, and all the urine passed till 10 a.m. was collected. The four hours specimen obtained by this means was examined for glucose by Fehling's test. On the two occasions on which there was slight reduction, the presence of glucose was confirmed by the phenylhydrazin test. On several occasions there was vomiting during the test period; these experiments were discarded. The glucose was dissolved in an amount of water corresponding with the quantity of milk the child was getting. If any was left this was measured and the actual amount of glucose taken was calculated. This explains why such varying amounts of glucose were given. The results are summarized in Table III. It is generally supposed that adults cannot tolerate more than 2·5 grm. glucose per kilo body weight (9). In the majority of my cases considerably more than this was given, and in the case of Se. 6·6 grm. per kilo were tolerated without glycosuria. In the two cases in which there was a trace of glycosuria, one, McV., received 3·1 grm. per kilo, and the other, Pr., received 3·0 grm. per kilo. In both cases the respiratory exchange was examined; in the case of the former the heat output was somewhat high, while in the case of the latter it was about what one would expect taking into consideration the difference between actual and expected weight. These results do not, in my opinion, show that there is lowered tolerance for glucose in atrophic children. Previous to these experiments, Muttill, Myer, and Sauer (11) showed that in seven atrophic infants whom they examined the tolerance for glucose injected into the blood-stream was higher than normal. These results are probably accounted for by the fact that in atrophy there is hypoglycaemia (3). In short, such children are in a state of sugar starvation, and, far from being unable to utilize carbohydrate, their tissues are able to utilize more than the normal amount.

Carbohydrate Absorption. The remaining possibility that there is defective absorption of carbohydrate from the alimentary tract must now be considered. It is generally recognized that large quantities of carbohydrate tend to produce enteritis in infants (3), but that they increase in weight more rapidly on a rich carbohydrate diet than on any other provided that the gastro-intestinal tract is not disturbed by this. It is possible that in atrophy the alimentary tract cannot digest carbohydrates efficiently, and that this leads to fermentation and gastro-intestinal disturbance. I am informed by Dr. Hutchison that in 102 cases of marasmus whose histories he examined there was a history of diarrhoea in 65 per cent. I have examined the clinical histories and weight charts of 16 atrophic children whose condition was diagnosed as fat dyspepsia, because it was found that their weight increased more rapidly on a diet of milk with a low percentage

of fat than on whole milk. In these cases the food value of the diet was brought up to requirements by the addition of carbohydrate. It was found that while they were in hospital loss of weight was associated with gastro-intestinal disturbances 22 times, and unassociated with gastro-intestinal disturbances 6 times. Moreover, during 775 days on which they were fed on a diet of whole milk, or on milk with a reduction of the normal amount of fat plus, in either case, 40 or more grm. of carbohydrate, they showed an aggregate increase in weight of 17·3 kilos, equal to a daily increase of 22 grm. During 665 days on which they were fed on whole milk or modified milk with less than 40 grm. of carbohydrate added per day, they only showed an aggregate increase in weight of 5·24 kilos, equal to a daily increase of 7 grm. These observations point to the conclusion that failure of the gastro-intestinal tract to deal with carbohydrates satisfactorily is an important factor in the production of atrophy.

From this investigation it would seem that two main factors are operative in the production of infantile atrophy, namely, extravagant utilization of nourishment and defective digestion and absorption of carbohydrate. But it seems to me that the second of these is the more important; for, provided the gastro-intestinal tract is in a condition to deal with it, there can be no difficulty in giving a diet of sufficient caloric value to supply all needs. This was done in the cases under examination, for the quantity of nourishment was regulated according to age and not according to actual weight. In the foregoing discussion it has been shown that it was ample for their requirements, for though atrophic infants have a heat output greater than normal per unit of actual weight (Chart V), it is less than the heat output of a normal child of the same age (Charts III and IV). In view of this and the fact that the respiratory exchange experiments show that in atrophy the essential constituents of the diet can all be normally utilized once they have gained access to the body, it would seem that failure of the digestive processes must be held responsible for the state of malnutrition in which the atrophic child carries on its precarious existence.

I have much pleasure in recording my sincere thanks to Dr. Leonard Findlay and Professors Noel Paton and E. P. Cathcart for invaluable help and criticism.

Conclusions.

(1) The respiratory quotients of atrophic infants do not suggest that their tissues are unable to utilize either fats or carbohydrates.

(2) The heat output of normal infants resting, but in the absorptive state, is between 50 and 60 calories per kilo per day.

(3) Infants whose weight is more than 65 per cent. of the expected weight for their age have as great a heat output as normal children. Those whose weight is less than 65 per cent. of the expected weight have a smaller heat output than normal infants of the same age, and the heat output gradually diminishes as the difference between observed and expected weight increases.

(4) It is suggested that in the first stages of atrophy the loss in weight takes place at the expense of metabolically inactive tissues, but that as atrophy advances there is wastage of metabolically active tissue.

(5) Evidence is brought forward which suggests that failure to thrive is not caused by inability of the organism to utilize any of the proximate principles of food, but rather by gastro-intestinal disturbances leading to defective absorption, especially of carbohydrates.

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CERTAIN EFFECTS OF PEPTONE INJECTIONS IN SEPTICAEMIA

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During the past 18 months several cases of puerperal septicaemia and of infective endocarditis have been treated at St. Bartholomew's Hospital by intravenous injection of Witte's peptone.

The behaviour of the leucocytes after such injections, and the alterations of pulse frequency and of blood-pressure which result therefrom, are of considerable interest, and it is with such effects that the present paper is concerned.

Nolf (1) advocated the use of intravenous injection of peptone in septicaemia and severe septic infection in 1917, reporting the clinical course of six cases of *Streptococcus pyogenes* septicaemia complicating war wounds, with one death, one case of puerperal septicaemia which recovered, and four cases of *Staphylococcus* septicaemia with one death. He also claims benefit from its use in other conditions due to infection, particularly typhoid fever (2), in which disease he had previously employed it, by intramuscular injection, to arrest haemorrhage and to prevent meteorism (3). Earlier still, in 1908, he had found that certain cases of haemophilia and paroxysmal haemoglobinuria were improved by subcutaneous or intramuscular injection of peptone. He further maintains (5) that intravenous injection of peptone, combined with the administration of salicylate by the mouth, renders the latter more efficacious in certain obstinate cases of articular rheumatism and enlarges the group of acute arthritis amenable to salicylate treatment.

Preparation of the Peptone Solution.

The solution of peptone for intravenous injection, as used in these cases, was prepared as follows:

0·5 c.c. of carbolic acid was added to 100 c.c. of hot, sterile, freshly distilled water. About 3 c.c. of this carbolic solution were added to 10 grammes of Witte's peptone, contained in a beaker, and the peptone made into a thick uniform paste by stirring with a glass rod; the paste was made thinner and thinner by the

slow addition of the remainder of the hot fluid. About 0·5 gramme of sodium carbonate was added and the whole brought to the boil, and stirred the while. The hot solution was filtered through a sterile filter-paper and funnel into a sterile 100 c.c. flask, and the filtrate heated for 20 minutes on the boiling-water bath. The flask, when cool, was sealed with a sterile rubber cap.

Dosage of Peptone.

In this series 8 or 10 c.c. of the 10 per cent. solution of peptone have been given as a rule at the first injection, and the dose was usually progressively increased by 1 or 2 c.c. The largest single dose was 18 c.c.

In the cases of puerperal septicaemia the injections were repeated at intervals of not less than 48 hours until the termination of the disease; in one case (Braddick) 10 injections were required, the last being of 14 c.c.

In only two of the injections to which reference is made (Weston 3 and 5) was the 10 per cent. solution diluted with normal saline, and in those only to 20 c.c. If signs of profound toxaemia—e. g. delirium, great restlessness, and anaesthesia to needle-pricks—are present, it is the writer's practice to give the peptone in 250 c.c. or so of Ringer's solution.

Of the five cases of puerperal septicaemia, the two fatal ones were fulminating, and died with general purulent peritonitis and pericarditis shortly after admission to hospital. No clinical improvement followed the injections in the cases of subacute infective endocarditis.

Technique of Injection and Record of Observations.

The requisite dose of peptone solution is drawn into a record syringe the metal plunger of which runs smoothly in the glass barrel. The syringe is then fitted with a needle not larger than No. 20, to avoid the risk attendant upon a too rapid introduction of peptone into the blood-stream. The injection of 10 c.c. should occupy at least 2 minutes.

If the injection is to be made into a vein in the left antecubital fossa, the haemocytometer pipettes, previously numbered, and cover-slips with marked pill-boxes to contain them, and the diluting fluid are set out on a small table on the left-hand side near the head of the patient's bed, within easy reach of the assistant who shall obtain samples of blood from the patient's left ear. The sphygmomanometer is adjusted to the right arm and is in charge of a second assistant. The third helper is the time-keeper who calls out the pulse frequency at the left wrist, while a fourth writes down the readings of pulse and systolic blood-pressure, as they are called out, every 15 seconds; he also notes the beginning and end of the injection, when a haemocytometer pipette is filled and when blood-films are made.

Before the injection is begun a pipette is filled, films prepared, and a few readings of the pulse frequency and systolic blood-pressure made. The blood-

pressure in each case was determined by the same method throughout,—either by palpation or by auscultation. In obtaining blood the ear is wiped dry before each observation; as a rule 9 counts were made in each of the later experiments, one before and eight after the injection was started.

Should there be a marked rise in the pulse frequency or any complaint of pain or discomfort by the patient, the injection is temporarily suspended, to be resumed, even more slowly than before, when such signs have moderated.

In the accompanying charts the period of time occupied by the injection is indicated by the thick black line at the top, and the time is calculated in quarter minutes from the moment when the injection is begun. Pulse frequency, recorded every quarter of a minute, is charted by the dotted line; the broken line indicates the curve of the blood-pressure, while the continuous line marks the course of the leucocytes.

Changes in Pulse Frequency and Blood-pressure.

An increase in pulse frequency and a fall in systolic blood-pressure occur, as a general rule, in consequence of the intravenous injection of peptone. In cases of septicaemia changes begin within half a minute of the commencement of the injection.

The higher the leucocytosis present the more pronounced is the disturbance, and the alterations are greater after a first injection than after subsequent ones, provided not more than 4 or 5 days elapse between them. Thus after a first injection a patient with 37,000 leucocytes showed a rise in pulse frequency of 18 beats per quarter minute and a fall in B.P. of 31 mm., in one with 20,400 leucocytes the pulse rose 5 beats per quarter minute and the B.P. fell 30 mm., while one with 16,400 leucocytes showed a rise of 5 and a fall of 22.

After the first injection the average fall in B.P. is 28 mm. in 2 minutes, whilst the pulse frequency increases 9 per quarter minute in $1\frac{3}{4}$ minutes. Following (or during) a second injection the corresponding figures are—fall in B.P. of 13 mm. in 2 minutes and a pulse rise of 3 per quarter minute.

The pulse frequency usually returns to the pre-injection figure within 3 to 5 minutes after early injections; with later ones there may be throughout little or no disturbance.

The blood-pressure takes longer than the pulse to return to its 'normal', and in later injections, although the immediate fall is apt to be less pronounced, it tends to be more prolonged and its curve to be less regular.

A certain 'tolerance' to peptone is therefore established, which is manifest in the curve of the pulse before it is seen in that of the blood-pressure. Hence it follows that although a rise in pulse frequency, which is easily determined, may be taken as an index of the fall in blood-pressure and of the general disturbance after a first or second injection, it is far less reliable as a guide to these happenings in later ones.

In one case (Weston) the changes outlined above were found to be reversed.

Shortly after the first injection had been started, the pulse frequency dropped considerably; the patient complained that she 'was going stiff all over' and had pain and tightness in the chest. Marked inspiratory dyspnoea rapidly developed, her face became flushed, then slightly cyanosed, and, a few seconds later, broke into a profuse perspiration, the pulse meanwhile remaining slow, but small. There was no exophthalmos. Only 6 c.c. were given and the discomfort was of short duration.

A second injection of 7 c.c. was given 2 days later. As before the pulse frequency at first showed a fall of 10 beats per quarter minute, but at the end of $2\frac{3}{4}$ minutes the pulse suddenly became impalpable at the wrist, and remained so until the 5th minute. At the same time the systolic blood-pressure, after a fall of only 6 mm., suddenly shot up from 114 to 160, to fall again rapidly to 110 (see chart Weston 2). The patient again had inspiratory dyspnoea, became very restless, and complained of severe pain in the lower lumbar and sacral region (but not in the chest), all of which symptoms passed off in the course of a few moments. Her blood at this time clotted so rapidly that it was impossible to fill the haemocytometer pipettes. In subsequent injections in which the dose of peptone was made up to 20 c.c. with normal saline, the blood-pressure curve resembles that of the other cases, but the pulse frequency, after an initial rise, still shows a fall. Slight shivering followed each of these injections.

In a case of infective endocarditis with leucopenia (B.) the pulse frequency shows but little variation, though the blood-pressure curve becomes more irregular with each of the four injections. The fourth, the only one which had any effect on his temperature chart, was followed by a rigor. (In an afebrile patient with arthritis and without leucocytosis, the first two injections of 8 and 10 c.c. at 48-hour intervals produced no appreciable alteration in pulse frequency and no rise in temperature, but a leucocytosis of 11,600 developed, and the third injection, of 12 c.c., was followed by a rigor and a temperature of 102° F.)

The Leucocytes.

A rapid diminution in the number of all forms of leucocyte in the peripheral circulation of a patient with leucocytosis results from the intravenous injection of peptone.

The 'low-water mark' of the leucocytes is reached between $1\frac{1}{4}$ and $3\frac{1}{2}$ minutes after the start of the first injection; there is a slight tendency for the leucopenia to take rather longer to develop in later injections, though it is none the less pronounced.

The degree of leucopenia produced by the injection shows a remarkable constancy. In the first injections of this series, though the count before injection varied between 16,200 and 37,000 per c.mm., the maximum and minimum lowest counts are 2,200 and 1,160 respectively, and the average rate of disappearance of the leucocytes is 2,300 per $\frac{1}{4}$ minute over a period of $2\frac{1}{2}$ minutes. In 21 injections the lowest count is between 2,000 and 4,000 in 15 and below 2,000 in 4.

Increase in the number of peripheral leucocytes begins immediately the fall is complete—sometimes apparently before the injection is finished. As a rule their reappearance is less rapid than their departure, but they exceed the pre-injection figure during the course of a few hours. In one instance (Knight 8) in which the injection was made five days after its precursor, 26,600 per c.mm. disappeared in 3 minutes, 23,200 returning during the next $4\frac{3}{4}$ minutes.

The start of the recovery is apt to be delayed by repeated injection, the angle of the curve gradually becoming less acute, but if more than 5 or 6 days elapse between the injections the angle tends again to become more acute—any 'tolerance' which may be developed is quickly lost.

In the absence of leucocytosis these changes are considerably modified. In a case (B.) in which the leucocyte count was 3,640 per c.mm. a fall of 1,000 per c.mm. only was observed to follow the intravenous injection of peptone (and the associated disturbance in pulse frequency and blood-pressure was considerably less than in those cases having a leucocytosis). A series of four injections, of 10, 10, 13, and 15 c.c., was given at four-day intervals, and by this means the total number of leucocytes was increased from 3,640 to 7,400, both polymorphonuclears and lymphocytes being involved in the rise. As the number of leucocytes in this case increased so was the fall in their number more pronounced as a result of the injection, and it is noteworthy that here also the 'low-water mark' lies between 2,000 and 4,000. No leucocytosis was noted after any of these injections, but the count after the fourth (B. 4) is peculiar in that it shows a rise at the half-minute from 7,400 to 11,800, followed by a fall in the succeeding half-minute to 5,000. Whilst it is possible that this isolated phenomenon is an error—no confirmation of it is to be expected from the differential count, as by the time films were made the number of leucocytes, if it did rise, had fallen to about the pre-injection figure—it is, perhaps, significant that in this instance the fall in blood-pressure, from 130 to 114 mm., is greater than after the preceding injections, and this is the only one of the four to be followed by a rigor, at the end of which the leucocyte count was 5,320 per c.mm. Six and twenty-four hours after the counts were 5,800 and 3,800 respectively.

That this leucopenia is not indicative of an indiscriminate imprisonment of all white cells irrespective of their class is shown by reference to the differential leucocyte counts.

(It is obvious that when alteration in the number of the peripheral leucocytes takes place with such rapidity, the total present when films are made is not the same as when the haemocytometer pipette is filled. As the coagulation time of the blood was generally so markedly diminished, the same drop of blood could not be used as a rule for filling the pipette and the making of films. In one instance only (Braddick 5) was the same drop used for both purposes; in the others the patient's ear was wiped dry after each observation, and the time noted at which films were made from a fresh sample of blood. This was usually found to be half a minute after blood was sucked into the haemocytometer, and the total number of leucocytes present when films were made was obtained by

calculation. This procedure may be open to criticism, but I consider a gross error is only likely to occur near the acute angle at the bottom of the curve, i. e. during the stage of profound leucopenia.)

The curves of the polymorphonuclear neutrophil leucocytes show the same features as do the corresponding curves of the total leucocytes—an immediate and abrupt fall followed by a slower rise; the widening of the angle in successive injections is well seen in the Knight series 1, 3–5. Between five and ten hours after an injection the number of leucocytes in the peripheral circulation may be as high as double the pre-injection figure, the increase being entirely in the polymorphonuclear cells. This added leucocytosis, when present, subsides within 24 hours.

The lymphocytes are not involved in the *débacle* so early as the polymorphonuclears, their departure when it sets in is apt to be less hurried, while the total diminution in their numbers is proportionately less.

Thus, in most instances the lymphocytes show little tendency to diminish before the end of the second minute. In second and later injections a progressive increase in the lymphocyte count during the first two minutes is often seen before the fall sets in (see Knight 3, 4, 5, and Braddick 2—in Braddick 5 I believe I was just too late to catch it). The lymphocytes also take longer to recover their numbers than the polymorphonuclears and no lymphocytosis ensues.

If the pre-injection lymphocyte count in puerperal septicaemia is below 1,000 per c.mm. the prognosis is, apparently, very grave.

Myelocytes, when present, behave much as the polymorphonuclear leucocytes; in one case only (Knight) were they encountered in appreciable numbers, being more numerous at the time of the second than at other injections, when their count fell from 4,800 to below 100 per c.mm. in $3\frac{1}{2}$ minutes. Their return to the peripheral circulation appears to be less rapid than that of the polymorphonuclears and lymphocytes.

In this series myelocytes (and normoblasts) were never found except when present to begin with, and in one instance only (Knight 1) were the myelocytes increased at the end of the experiment; before the injection they numbered 208, rising to 1,014 at six minutes, and 3,600 at the 5th hour.

The numerical changes in the polymorphonuclears and lymphocytes are strictly comparable to those which follow the intravenous injection of coli-typhoid vaccine (6), but with peptone the cycle occupies minutes, whereas with the former hours are consumed. Coli-typhoid vaccine appears to have a more 'stimulating' effect on the haemopoietic system than peptone, for in the leucocytosis which follows the intravenous injection of the former myelocytes are frequently found and normoblasts not seldom.

Alterations in the leucocyte count and blood-pressure, similar to the above, are described as occurring in dogs as the result of peptone injections by Biedl and Krause (17), who comment on the analogy between anaphylactic shock and the toxic effects of Witte's peptone. Dale and Laidlaw (16) found leucopenia to be present in histamine shock in cats, but do not regard the phenomenon as having

any special significance, 'since we have observed a leucopenia of the same type as a result of a prolonged fall of blood-pressure produced in other ways, e.g. by complete pithing or by slow infusion of acetyl-choline'. In man, however, this cannot apply, for the degree of leucopenia following peptone injections is in no way related to the magnitude or duration of the fall in blood-pressure.

The first reference to leucopenia following injections of peptone is by Samson-Himmelstjerna (7) in 1882. Several workers, amongst whom are Loewit, Delezenne (8), and Wright (9), maintained that peptone brought about an actual destruction of the leucocytes. Athanasiu and Carvallo (10) considered that in virtue of heightened amoeboid movements the leucocytes left the vessels of the splanchnic area by diapedesis. Bruce (11) showed that, in rabbits, the leucocytes in the lung and spleen were greatly increased in numbers. Nolf (12) found that in dogs in which the aorta and inferior vena cava are occluded above the diaphragm, the arterial pressure and leucocyte count in this 'limited circulation' show the same changes as in the normal animal, though in lesser degree. These phenomena are accentuated if the obstruction to the vessels is removed a short time after the injection, and he considers the leucopenia is due to the retention of the leucocytes in the abdominal vessels, the wall of which has suffered from the action of peptone. Peptone has no leucocytolitic action *in vitro*.

Coagulation of the Blood.

In each of these experiments the coagulation time appeared to be distinctly diminished during, and for a short time after, the injection.

The blood platelets, though not enumerated, were noticed to be present in large numbers in all films, though their numbers perhaps diminished with the rising polynuclear tide. No estimation of the coagulation time was made, but considerable difficulty was experienced on several occasions in filling pipettes and making blood films owing to the rapidity with which clotting took place. In one instance (Weston 2), between the 3rd and 7th minutes the blood clotted in the haemocytometer pipette before the diluting fluid could be sucked up.

This decrease in coagulation time is found also in animals to result from the slow injection of small doses, whereas the rapid injection of peptone into the circulation of rabbits, dogs, and guinea-pigs increases the coagulation time of the blood. Novy, DeKruif, and Novy (13) have shown that the symptoms and findings after the rapid injection of peptone into rabbits and guinea-pigs are the same as those produced by anaphylatoxin, by agar, or in specific anaphylactic shock—dyspnoea, spasms, convulsions, incontinence, and, in addition, a marked exophthalmos. Contejean, Hedon, and Delezenne maintain that the injection of peptone into a dog deprived of its liver does not produce incoagulability of the blood. Nolf (12) has shown that in dogs in which occlusion of the aorta and vena cava has been produced above the diaphragm the blood remains coagulable after injection of peptone into the jugular vein, but fibrinolysis takes place in time. If the obstruction to the vessels is removed a short time after the injection

the blood becomes incoagulable. He considers the fibrinolysis observed in the blood in the 'limited circulation' must be due to the action of a substance secreted by the vessel wall.

Starling (14) found that, after intravenous injection, peptone is rapidly transferred from the blood-stream to the lymph by selective activity of the endothelial cells of the vessel wall—though it does not disappear from the blood of dogs more rapidly than any other abnormal constituent—so that shortly after injection the lymph contains more peptone than the plasma itself. But there is no connexion between the loss of coagulability induced by the intravenous injection of peptone and the amount of that substance present in the plasma at any given time.

Red-cell counts, made with a view to determining any marked loss of plasma during these experiments, invariably showed a slightly higher figure after an injection than immediately before it, though the difference was not more than might be accounted for by experimental error. Peptone is a powerful lymphogogue in animals; Starling (15) considers the increased flow of lymph is due to heightened permeability of the wall of the hepatic capillaries, as, in dogs, nearly the whole of the extra flow of lymph is derived from the liver.

It may be mentioned that no albumose was found in the urine withdrawn by catheter, in several of my cases, two and four hours after the injections.

Conclusions.

1. The intravenous injection of Witte's peptone in therapeutic doses produces an immediate rise in pulse frequency, fall in blood-pressure, leucopenia, and diminution in the coagulation time of the blood, all of short duration.

2. These phenomena are all more marked in patients with leucocytosis.

3. A 'tolerance' to peptone, as regards pulse and blood-pressure, is soon established, but such tolerance is of short duration.

4. The polymorphonuclear leucocytes show a rapid fall followed by a slower rise. The fall in the lymphocytes is proportionately less, is relatively delayed, and may be preceded by a rise.

5. The leucopenia is followed by a transient polynuclear leucocytosis.

6. The changes are similar in kind to those following the intravenous injection of coli-typhoid vaccine, but peptone has a less 'stimulating' effect on the bone marrow.

In carrying out these observations I have had several helpers to whom I am greatly indebted, especially to Sisters Casualty and Mark. The puerperal cases were under the care of Drs. Barris or Donaldson, and to them I make my acknowledgements. My thanks are due particularly to Sir Archibald Garrod, who has stimulated me with his interest, suggestions, and advice.

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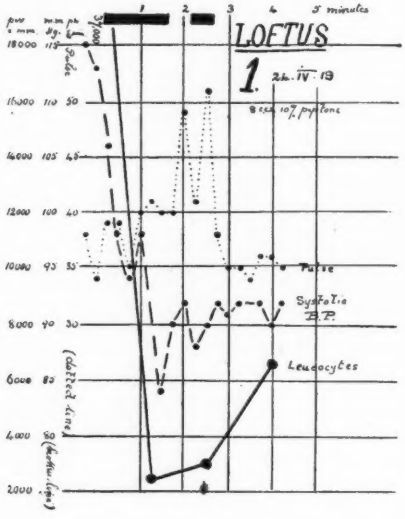
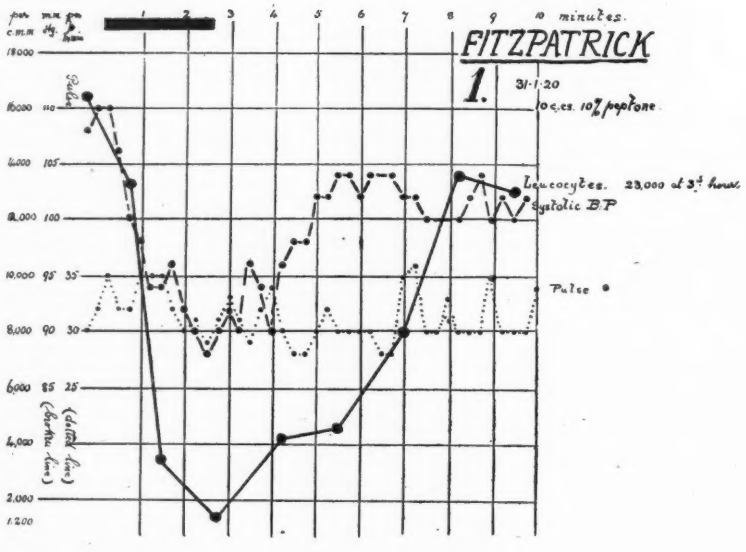
Charts illustrating Changes in Leucocyte Count, Blood-pressure, and Pulse Frequency.





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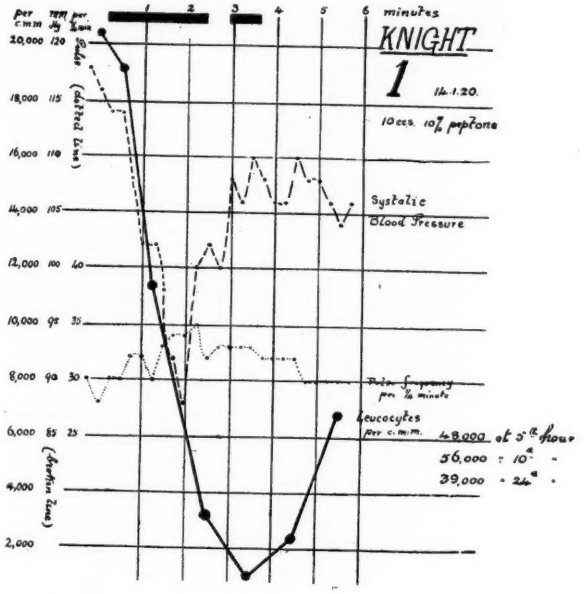

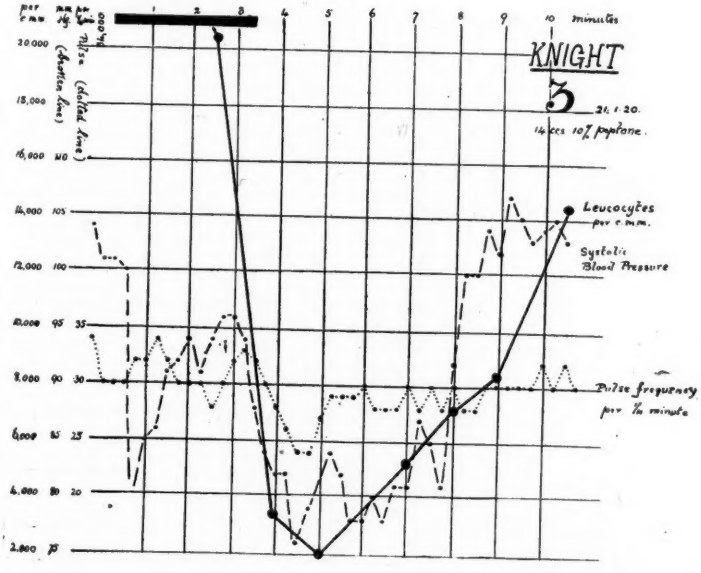

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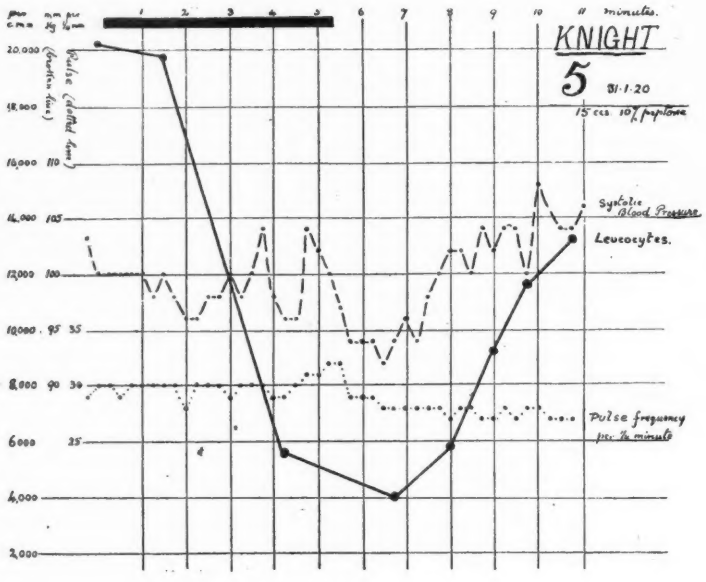

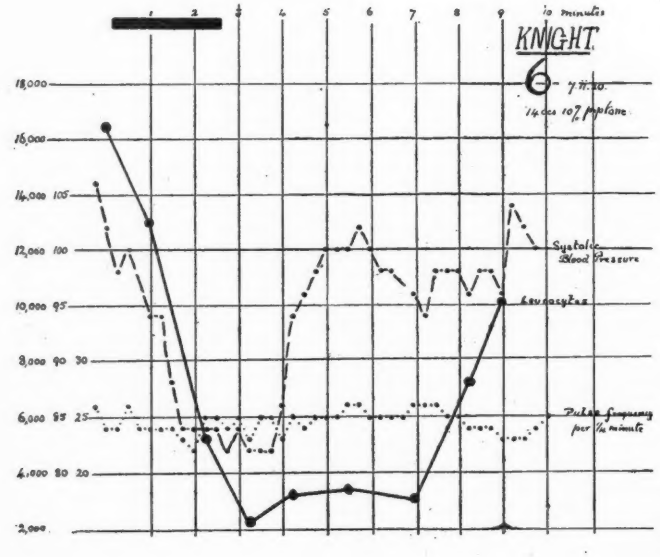

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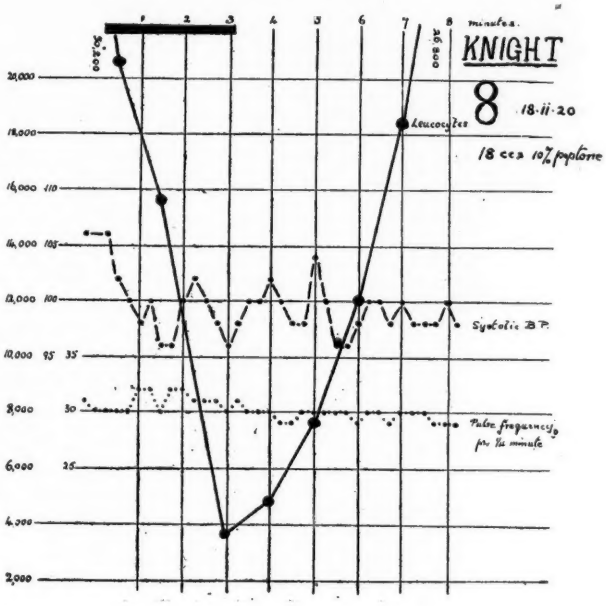

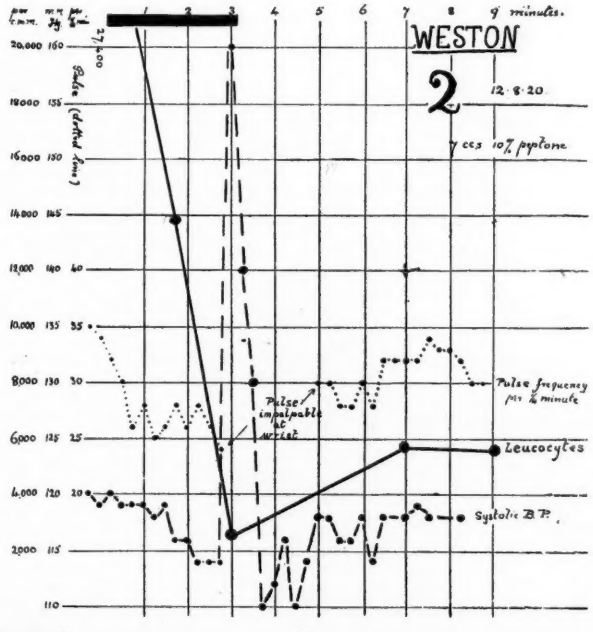

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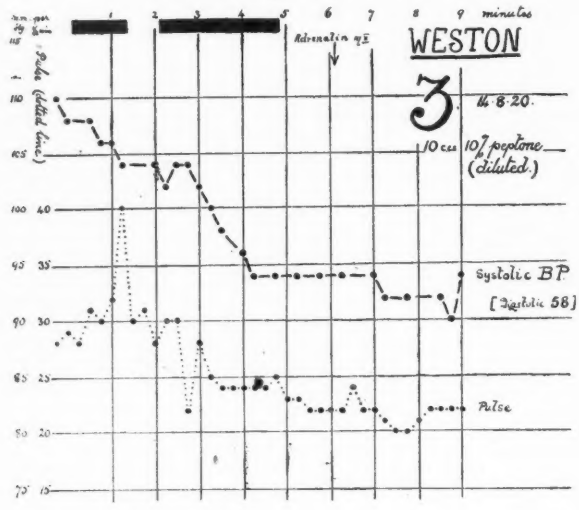

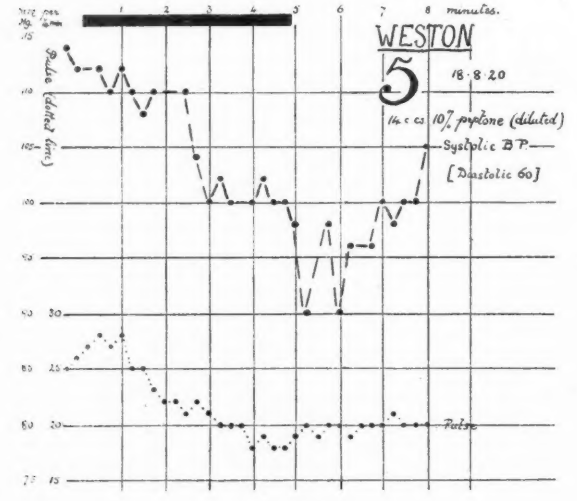

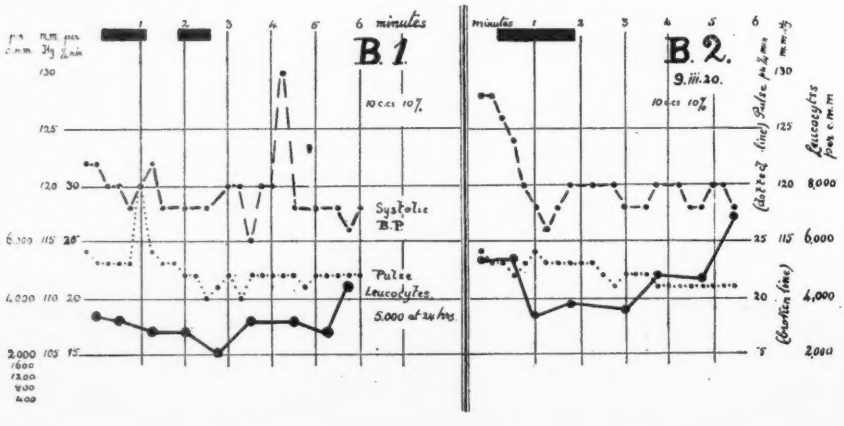

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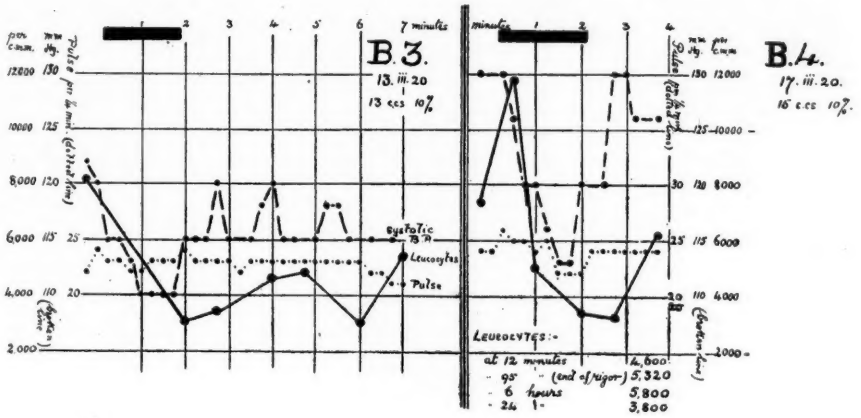
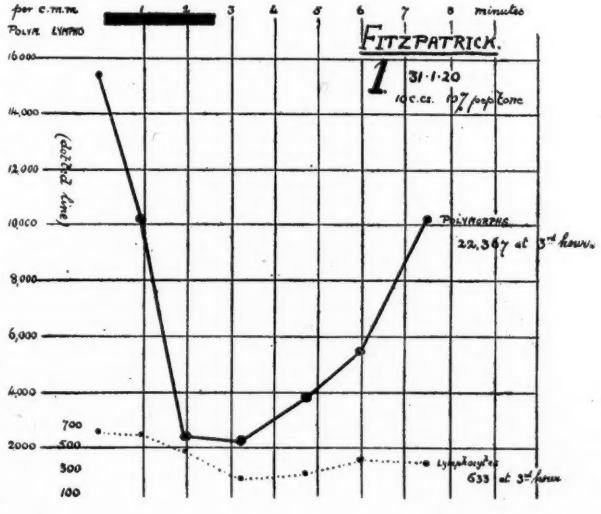


Charts illustrating Changes in Lymphocytes and Polymorphonuclear Leucocytes.



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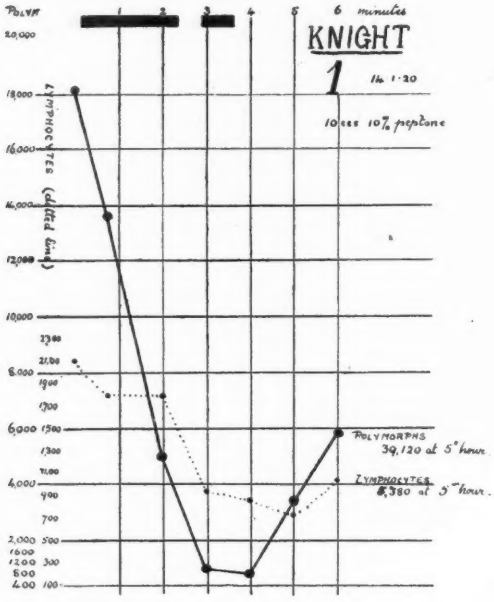
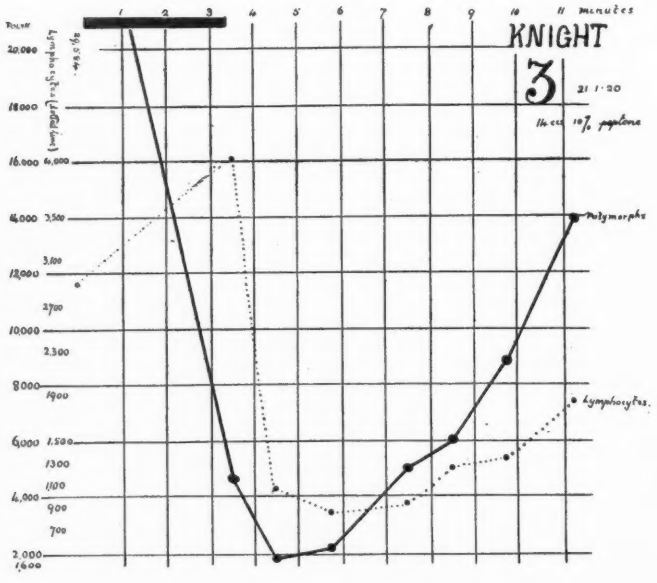
Charts illustrating Changes in Lymphocytes and Polymorphonuclear Leucocytes.





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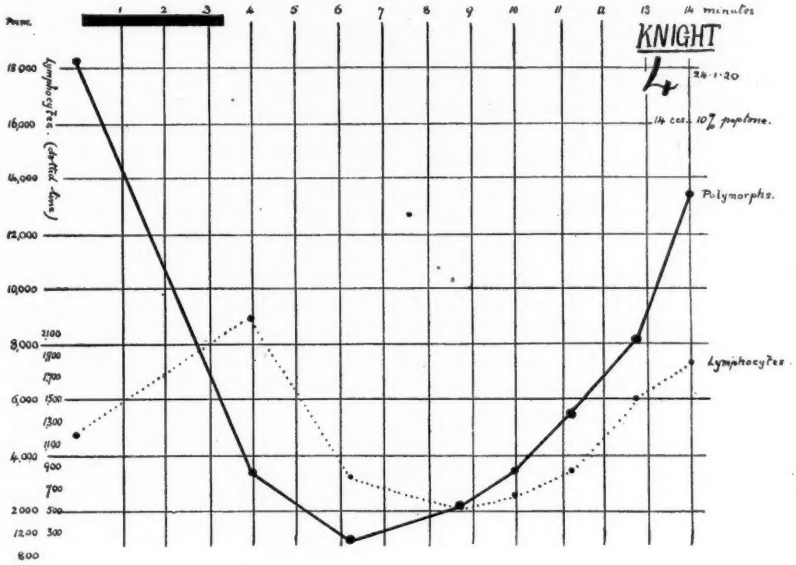

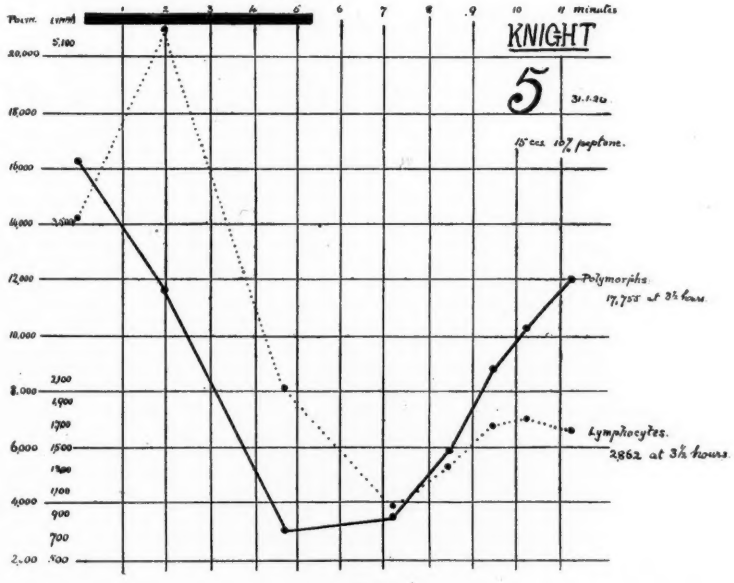

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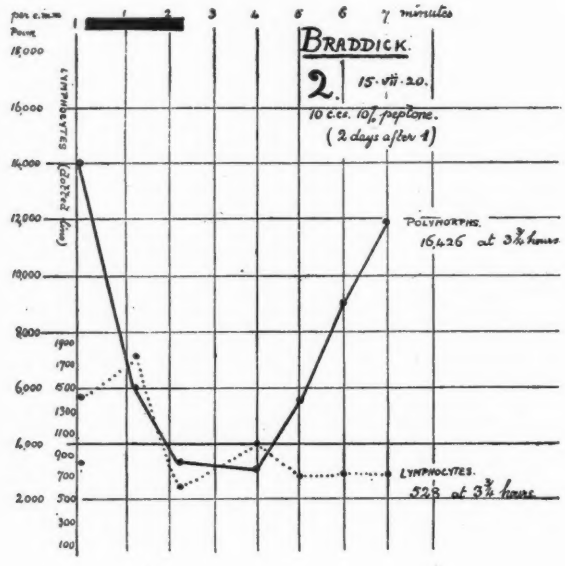

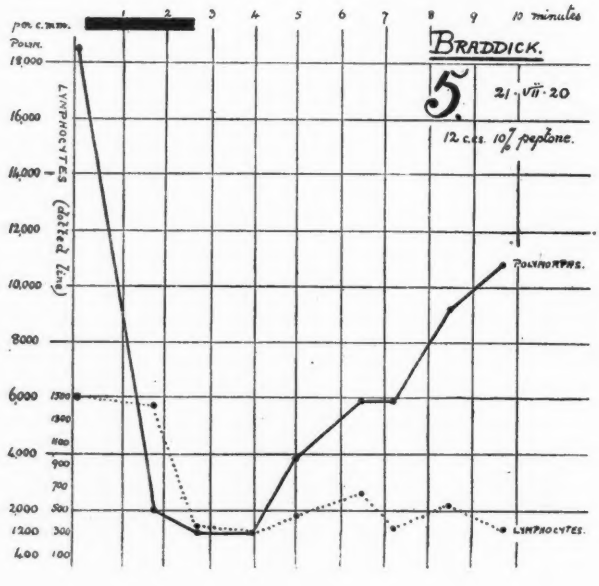

RENAL DWARFISM

By HUGH BARBER

(From the Wards and Clinics of the Derbyshire Royal Infirmary)

With Plates 1 and 2

THERE is a form of interstitial nephritis in children which gives rise to dwarfism and very probably to bone deformities. The want of development and deformities of bone may be the most obvious symptoms, and not infrequently are the conditions for which the parents seek advice; so that the name of Renal Dwarfism is a suitable designation for this type of case, which may present itself clinically as a variety of late rickets.

In 1911 one such patient was attending my Out-patients' department when I saw the notes of a case shown by Dr. Miller at the Royal Society of Medicine. Dr. H. Morley Fletcher had first described this condition; and similar ones have been shown since at the Children's Section. In discussing the want of development the term Infantilism has been used; and four cases from this hospital, published in 1913 and 1918, were discussed from this point of view; but in January, 1920, when I published three more, Infantilism would not meet the case, although the want of development in size was quite as marked, and I used the term Renal Dwarfism. Dr. D. H. Paterson, showing three cases in April, 1920, with very complete notes, has collected all the references, and in acknowledging the name of Renal Dwarfism has adopted it.[1]

Three more recent cases enable me to discuss ten in all; and I think it may be of general medical and surgical interest to embody their chief features in one paper.

DEFINITION. A condition of stunted development, associated with bone deformities of the late rickets type, due to an insidious chronic interstitial nephritis, of obscure aetiology.

[1] I have, however, just come across a paper by Mr. Clement Lucas in the *Lancet* in June, 1883, entitled 'A Form of Late Rickets associated with Albuminuria', where he says that he has learned 'that the phenomena of late rickets and albuminuria are too frequently connected to be matters of chance'. He regards the albuminuria, however, as functional, and does not record the quantity of urine, or the specific gravity. Nor is there much evidence of the course of the disease, or any suggestion of its serious nature. But it is strange that his observation of this association of albuminuria and bone deformities does not appear to have been confirmed for nearly thirty years.

Aetiology. In sex the cases have been equally divided—five boys and five girls. I can find no evidence of antecedent disease as a disposing cause, although I have obtained good histories in most cases. There have been no signs of congenital syphilis, and only one positive Wassermann result, out of six cases tested. There is no evidence of any symptoms which might suggest that the interstitial nephritis is preceded by any parenchymatous disease of the kidneys. Nor would it seem to be secondary to pyelitis.

The family histories have shown no unusual features; other children of the same parents have been well developed; and the obstetric histories of the mothers not abnormal. The isolated remarkable feature is the fact that Cases II and III were brother and sister, next in age. There were six older healthy children, then Case II was number seven, Case III was the eighth child; and the youngest child, aged 9 years, could look over the heads of these two, aged respectively 15 and 13 years.

The long time during which symptoms may be absent, and the early age at which they have been noticed in some cases, would admit of the explanation that the disease is due to some intra-uterine infection. However, the cause of the condition is very obscure; it would seem to be a slowly progressive fibrosis of the kidneys, limited to the interstitial tissue, beginning quite early in life, with much less tendency to produce changes in the systemic blood-vessels than is the case with other forms of interstitial nephritis.

Morbid Anatomy. Only five post-mortem examinations have been obtained, but the findings have been similar in type, varying a little only in degree. The kidneys are very small; the smallest weighed 120 grains in a boy of 15, and the largest 300 grains in a boy of 16. The capsule is not adherent, the surface is only slightly granular or irregular; it is pale with a little mottling; a few cysts may be present; the cortex is narrow and the cut surface pale; the blood-vessels do not stand out. Microscopically there is interstitial nephritis, varying in degree with the size of the kidney. I submitted the section of the kidney shown in Fig. 3, Plate 2, to Dr. P. P. Laidlaw, of Guy's Hospital, who kindly reported as follows: 'The dilated tubules show very thin and flat epithelium; the cells lining the tubules do not seem to show much progressive change; the glomeruli, although a few of them show adhesions to the capsules, are, on the whole, fairly normal; the capsules are also dilated. The bulk of the change seems to be singularly limited to the interstitial tissue, and here the change is progressive. The arteries in the kidney, especially the smaller ones, show well-marked thickening.' The heart has been normal, although, perhaps, showing a little hypertrophy of the left ventricle, considering the small size of the child; the aorta normal; and sections of the brachial artery in the most severe case were normal. The thyroid, suprarenals, and pituitary have been normal, as also the brain, the liver, pancreas, and other organs.

Symptoms. In a *typical case* the child usually has been described as small since birth, but nothing very noticeable in most cases until about 6 or 7 years of age, after which development has been very poor. Some degree of thirst is

usually present, and with it polyuria. As the child grows older the dwarfism becomes more obvious, and deformities of bone tend to develop, more particularly genu valgum, towards the age of puberty. A fatal termination from uraemia would seem to be most probable some time in the second decade.

Onset. The onset is very insidious. Five of the cases were obviously stunted, with bone deformity, before medical advice was sought. Case VII, an obvious renal dwarf when admitted for genu valgum, aged 13 years, was in this institution, ten years previously, diagnosed as diabetes insipidus, with urine free from albumin. Case VI attended the Out-patients' department of one of my late colleagues for 'weak action of the heart and blue hands' when aged 6 years; the urine was not examined; she returned with characteristic signs of renal dwarfism seven years later. Case V I saw, aged 12½ years, with thirst and polyuria; the diagnosis of interstitial nephritis was made, but, after three attendances I lost sight of him for three and a half years, when he returned with recently developed genu valgum. Case III, diagnosed at my Out-patients' department, aged 12 years, had been an inmate of this institution for a 'cold abscess' five years previously, with urine of sp. gr. 1,010 and albumin present three times in four examinations. One would conclude that the kidney lesion was present quite early in life, perhaps in infancy. The disease must be overlooked fairly frequently, because the bone deformities do not develop till towards puberty; and the signs and symptoms more suggestive of interstitial nephritis may not be very obvious.

Thirst and *polyuria.* In two cases thirst was as striking as in a case of diabetes insipidus. In six others it was pronounced, but not always brought to light without inquiry. Two cases, which ended fatally, showed little signs of thirst.

The urine. The urine varies with the degree of disease, but is pale in colour in all cases, with specific gravity usually between 1,004 and 1,008 in the Out-patients' department, perhaps tending to be slightly higher in the ward, but the highest record was 1,014; and this was an isolated reading, quite exceptional. The total quantity passed in twenty-four hours has been, perhaps, the most variable feature, obviously, to some extent, related to the polydipsia. An average amount for the children about puberty who have not suffered from distressing thirst has been 40 to 50 oz., but one patient with marked polydipsia passed 6 or 7 pints per diem.

Albumin has been present in all cases except one. Usually about 1 part per 1,000. It has not varied much with rest or exercise, and has always been present in the Out-patients' department; but two cases while in the ward for observation were each free from albumin on two occasions out of twenty-two and thirty observations respectively. The one exceptional case, in which albumin was *not* found, unfortunately, was only tested as a routine by a nurse before operation. However, another case with albuminuria when I saw her, aged 13 years, was diagnosed as diabetes insipidus with no albuminuria ten years previously. The question of albuminuria will come up again under 'Diagnosis'

A few hyaline casts have been found; but never any evidences of parenchymatous disease, or any blood.

Cardio-vascular signs. These have been very slight. It has not been possible to demonstrate any definite thickening of the radial arteries. The brachial and femoral arteries in one or two cases may have been slightly thickened, but not much. Haemomanometer readings have been normal. There has not been obvious hypertrophy of the left ventricle, nor accentuated second sound. There were no haemorrhages, and no oedema. The optic disks were examined in one or two cases; there were some signs of old retinitis in Case II, which *post mortem* showed the most extreme fibrosis of the kidneys. The blood examinations have shown nothing abnormal.

Blood pressure. The maximum systolic blood pressure has been recorded in nine cases. It has usually been about 100 mm., the highest reading 110 mm. in the one patient who has reached the age of 20 years. I believe other observers have usually found the haemomanometer readings to be normal, but there have been some exceptions. In my cases the absence of signs of increased blood pressure has been very striking.

Facial aspect. There has been something of an unhealthy earthy pallor, but no marked anaemia.

Mentally. The children have been quite intelligent in most cases.

Headache. Has been complained of, but has not been very severe.

Dwarfism. The stunted growth is very striking. The children are usually described by the parents as small since birth, but more noticeably so after 6 or 7 years of age. One case I only saw *post mortem*, and two others died unexpectedly soon; but all three were striking cases from this point of view. The actual figures for the height of the remaining seven cases are as follows; they are tabulated in age order:—

1	Renal dwarf	aged	13	years	=	9	inches	below	the average height.
2	„	„	13¾	„	=	10	„	„	„ „
3	„	„	14	„	=	9½	„	„	„ „
4	„	„	14	„	=	5	„	„	„ „
5	„	„	16	„	=	10	„	„	„ „
6	„	„	16	„	=	16	„	„	„ „
7	„	„	17	„	=	11	„	„	„ „
The same case		„	20	„	=	12	„	„	„ „

(For the average height I am taking Dr. Duke's table for artisan class, in Allbutt's *System of Medicine.*)

Other children of the same parents have been well up to, or above, the average height; as I have been able to illustrate in two published photographs, and in Fig. 2, Plate 1.

The weight has been more or less in proportion to the height, but the children are thin, and tend to become more so as the condition progresses.

One case died, aged 15 years, with a want of general and sexual development,

which justifies his inclusion as a case of infantilism; and several others, between the ages of 12 and 14, showed no primary or secondary sexual characteristics. The term infantilism has been used in connexion with these cases by most observers; but, apart from the fact that it is not a very satisfactory word, it is unsuitable because renal dwarfs equally stunted may have sexual development, which is illustrated by both the cases whose photographs appear in this article. Fig. 1, Plate 1, is of a girl in whom menstrual periods developed at the age of 13 and have continued regularly for twelve months; and the case Fig. 2 has sexual development, although the periods only come three or four times a year.

Bone deformity. Deformities of bone, of which genu valgum is the most definite, have been present in eight of the ten cases. The most interesting point is the age at which this genu valgum develops. In one case it was at the age of 17½ years; in four it was between 14 and 15 years of age; in the other three about 13 years, 11½, and 10½ years respectively. I have very definite histories on this point, corroborated by other witnesses besides the parents in some cases; and one of my cases was diagnosed, aged 12½ years, as a renal dwarf, 8 inches below the average height, with straight legs, and he returned, 3½ years later, on account of recently developed crooked legs.

According to the histories it would seem that the genu valgum develops comparatively quickly. The changes seem to be similar to those of rickets; the knees and wrists are most noticeably affected, but X-ray pictures have demonstrated similar disease in other joints, for example, the ankles; and swelling has been palpable at the junctions of the ribs and costal cartilages. Major Milner's X-ray report has been: 'Increase in the size of the proliferation zones, the normal translucent line greatly increased in breadth, not only enlargement, but great irregularity and want of definition due to irregular calcification.'

Course and termination. The insidious onset and evidence of the insidious nature of the symptoms have been discussed. A fatal termination from uraemia is probably inevitable. But on clinical grounds alone it is very difficult to foretell the course of the disease. It is not possible to estimate with certainty the length of time that a serious degree of interstitial nephritis has been present; but one case I observed for seven years; another case, still living, I diagnosed five years ago, aged 12½ years, and the case shown in Fig. 1, still alive, was supposed to have diabetes insipidus eleven years ago. By way of contrast two cases, aged respectively 11 and 15 years, which, not at all obviously ill, came up for dwarfism and genu valgum, were taken in for observation, and developed fatal uraemia in a week or two. The first of the series is also a case in point, for he died ten days after an osteotomy, and was only diagnosed *post mortem*.

The ages at death in the seven fatal cases have been 11 years, 14 years, 14 years, 15 years, 15 years, 16 years, and 16 years. Fig. 2 shows an exceptional case, in the fact that she is the eldest, still alive, aged 20; and one other is alive at 18 years of age.

Diagnosis. The diagnosis is quite obvious when all the signs are present about puberty; but in earlier life the condition may easily be overlooked.

(*a*) Before bone deformities are present. Diabetes insipidus, or bilateral cystic disease of the kidneys, may give rise to a similar urine, and to polydipsia, when the presence of albumin is the only distinguishing feature. This albuminuria would seem to be fairly constant by the time a case is likely to come under observation; but it has been absent occasionally on one or two isolated days, and, as stated above, it was not detected in one case examined as a routine before operation. It is unfortunate that this exceptional one should have received so little attention; but it was the first case recognized here, and was only diagnosed *post mortem*. However, Case VII was diagnosed as diabetes insipidus, with polyuria observed free from albumin over several weeks, when 3 years old. She was an obvious renal dwarf, with albuminuria, ten years later. That albumin may be absent, and so complicate the question, seems reasonable to suppose; and Dr. Cameron mentions such a case. I have not been able to gain any assistance from palpating the radial arteries, which I think has been the case with other observers. I am not so sure about the brachial and femoral arteries; but any changes are by no means obvious. Examination of the heart has not revealed hypertrophy of the left ventricle, or any accentuation of the second sound. Haemomanometer readings have not been above the normal.

(*b*) When bone deformities are present. If the urine is characteristic of interstitial nephritis there is no difficulty. But cases conforming to the type which clinically may be called late rickets, in which there is no polyuria or albuminuria, may be difficult problems, because interstitial nephritis might be in an early stage. In three such cases, where I think kidney disease may be *excluded*, the radiograms have shown less irregularity of ossification at the epiphyseal lines; but, although the radiogram of the affected joints in renal dwarfism appears to be quite a characteristic picture, I have not seen enough by way of contrast in other forms of late rickets to assess the value in diagnosis.

PROGNOSIS. There seems to be little prospect that the condition will be arrested; a steady progress is the rule, with a fatal determination probably somewhere in the second decade. But, on purely clinical grounds, it is difficult to estimate how near such a termination may be.

A more complete investigation by testing the urea content of the blood, and tests of the kidney efficiency, such as the urea concentration test, may make the prognosis less uncertain and help also in diagnosis in the early stages.

TREATMENT. There would seem to be little scope for treatment. Thyroid and other glandular extracts have had no effect. Surgical interference for genu valgum is not advisable, and is likely to precipitate, or, on account of the uncertainty of the future, to appear to precipitate, an attack of uraemia. But by the light of the experience of these cases I think some sort of support for the legs might be devised with benefit if the patient is seen before genu valgum has developed. Case V is an example in point. He was diagnosed, aged 12½ years, with straight legs, and at 18 years of age he is still alive, able to push a small barrow, but is much handicapped by very crooked legs.

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There appears to be no account of this condition in medical text-books. The most complete account of published cases, with references, is given by Dr. Paterson in the *Proceedings of the Royal Society of Medicine: Children's Section*, 1920. In the *Proceedings, Children's Section*, the condition has been discussed in the following numbers:—1911, iv; 1912, v; 1920, viii; 1920, ix.

The cases that have been shown at various meetings have been similar in type to these described above; but in one, or perhaps two, bone deformity was present early in life. This, however, appears to be quite exceptional. And some of the cases have shown cardio-vascular changes with increased blood-pressure. I think it is possible that the kidney disease is of a different type in such cases with either a different aetiology or an additional aetiological factor.

Synopsis of Cases.

Cases I, II, and *III* appeared in the *Brit. Med. Journ.*, November, 1913.
Case IV appeared in the *Lancet*, January, 1918.
Cases V, VI, and *VII* appeared in the *Lancet*, January, 1920.

Case I. Boy, aged 16 years, much under-sized, but not infantilism; admitted for genu valgum of recent origin. Urine examined before operation pronounced free from albumin. Osteotomy performed; patient died ten days later of uraemia. *Post mortem*, the kidneys showed typical interstitial nephritis, weighing 300 grains each.

Case II. Boy, died of uraemia, aged 15 years. *Post mortem*, the kidneys showed extreme degree of interstitial nephritis; the right weighed 120 grains, the left 220 grains. The other organs were normal. He had been under observation since 7½ years of age, when he was brought up for want of development and thirst. His development was reported fair until 5 years of age. When 14 years old he was 9½ inches below the average height, with characteristics of infantilism, but no bone deformities. Thirst and polyuria were extreme for the 7½ years during which he attended; urine sp. gr. 1,003 to 1,006, average quantity per diem about 6 pints, albumin constantly present. Blood-pressure normal, and no thickening of radials.

Case III. Girl (sister of Case II), died of uraemia, aged 13 years. Was in this hospital, aged 7 years, with 'cold abscess' of thigh. The urine was examined four times, albumin being present on three occasions; sp. gr. 1,010. She was brought up five years later (aged 12) for thirst and headaches. Urine sp. gr. 1,004; albumin present. Height 9 inches below the average; no bone deformities; no signs of sexual development. She died of uraemia a year later.

Case IV. Boy, aged 16 years, came up on account of genu valgum. Always

small, but quite bright and active at school. The legs became crooked at the age of 14½ years. He was 16 inches below the average height, with want of development almost amounting to infantilism. Urine sp. gr. 1,005; albumin present, quantity 51 oz. per diem. Slight thirst; arteries not thickened; systolic blood-pressure 100 mm. He died a year later. *Post mortem*, kidneys typical; other organs normal.

Case V. Boy, aged 12½ years, attended for thirst and polyuria. Arteries normal; systolic blood-pressure 100 mm. Urine sp. gr. 1,006; albumin present. Height 5 inches below the average; no bone deformities. He attended for three months and was then lost sight of. His next attendance was 3½ years later, aged 16 years, for recently developed genu valgum. He had been at work regularly as errand-boy, but stated that he went to bed for four weeks with 'influenza' and when he got up his legs were crooked. He was now 10 inches below the average height. The urine was unchanged. His condition has altered very little in the two years since, and he is still alive, aged 18 years.

Case VI. Girl, aged 13¾ years, admitted for dwarfism and genu valgum which developed at the age of 13 years. Height 10 inches below the average. Urine sp. gr. 1,004; albumin present, quantity 41 oz. per diem. Systolic blood-pressure 90 mm. She had always been small, but development especially poor since 6 or 7 years of age. She attended a late colleague's Out-patients' department, when aged 6 years, for 'weak action of the heart and blue hands'; the urine was not examined. She changed very little while under observation, and died of uraemia, aged 14½ years. *Post mortem*, kidneys typical (see Fig. 3, Plate 2); other organs normal.

Case VII. Girl, still alive (see Fig. 1). She was an inmate of this institution, aged 3 years, with 'diabetes insipidus'; urine sp. gr. 1,008 to 1,010, was examined many times for albumin with negative result. She contracted scarlet fever, and was removed to the Isolation Hospital. She has always been thirsty, and the legs weak, but otherwise normal; and has passed through an attack of measles. Aged 13 years, she was admitted to the surgical side for genu valgum, which developed at 11½ years of age. Urine sp. gr. 1,008; albumin present, quantity 50 oz. per diem. Radial arteries normal; systolic blood-pressure 100 mm. Her present age is 14 years; height 5 inches below the normal. The knees, wrists, and ankles are affected. Pubic hair was present at 13 years of age; and regular menstrual periods have appeared for the last twelve months.

Case VIII. Girl, still alive, aged 20 years (see Fig. 2). First attended, aged 17 years, for stunted development and thirst. Height 11 inches below the average. Sexual development fairly normal. Urine sp. gr. 1,010; albumin present on two occasions out of four examinations. No bone deformities present. I have looked her up recently. She is now 20 years of age, 12 inches below the average height, with genu valgum, which developed about 17½ years of age. Menstrual periods began about 18 and come every few months. Urine sp. gr. 1,006; albumin present. Systolic blood-pressure 110 mm., radial arteries normal, but the brachials and femorals appear to be a little thickened. X-ray pictures do not show much

change as the epiphyses are united. She is not wasted. She has always been delicate; has not had scarlet fever, but after measles, aged 4 years, she seemed to fail in health.

Case IX. Boy, aged 15 years, attended for renal dwarfism. Has always been small and delicate; thirst since 6 or 7 years old. No history of scarlet fever, but measles, aged 4 years. Legs became crooked six months before admission. Urine sp. gr. 1,005 to 1,010; albumin constantly present, quantity 50 oz. per diem. X-ray photographs showed changes in wrists and ankles. He died of uraemia in four weeks.

Case X. Girl, aged 11 years, attended for renal dwarfism. Has always been small; thirst since a baby. No history of infectious disease. Genu valgum developed recently. Urine sp. gr. 1,005; albumin present. She died of uraemia twelve days after her first attendance. *Post mortem*, kidneys typical; other organs normal.

FIG. 1
Renal Dwarf aged 14 years (Case VII)

FIG. 2
Renal Dwarf aged 20 years (Case VIII) with sister aged 16 years

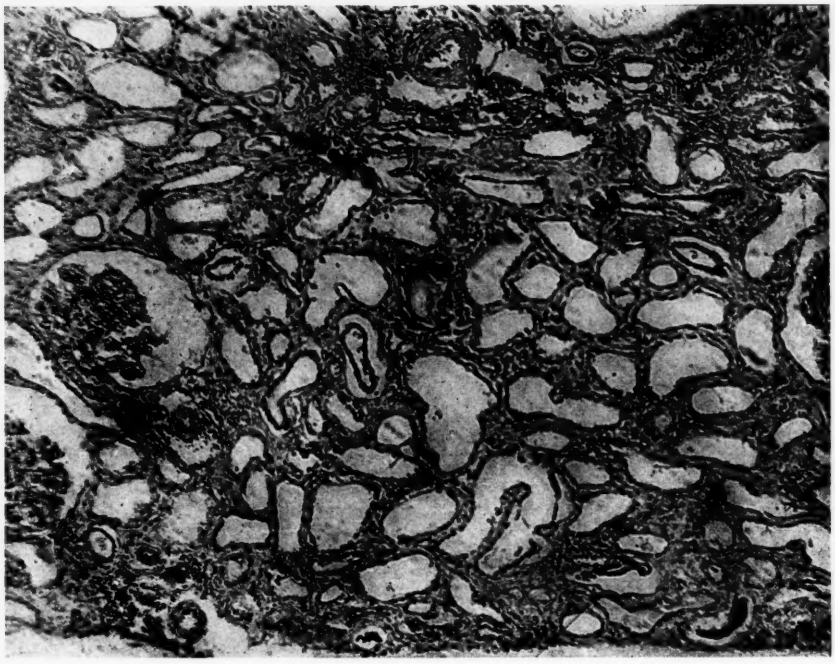

FIG. 3
Microphotograph of Kidney (Case VI)

FIG. 4
Radiogram typical of Renal Dwarfism (Case VI)

A CONTRIBUTION TO THE STUDY OF ARTERIO-SCLEROSIS, WITH SPECIAL REFERENCE TO ITS RELATION TO CHRONIC RENAL DISEASE

By GEOFFREY EVANS

With Plates 3–10

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[Q. J. M., April, 1921.]

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Introduction.

In this contribution to the study of arterio-sclerosis the type of arterial disease first described by Gull and Sutton (1) as arterio-capillary fibrosis, and more recently named diffuse hyperplastic sclerosis, forms the main object of study. The subject has been simultaneously approached from pathological and clinical aspects. The pathological section aims at defining the nature and distribution of the vascular lesion, and in the second part of this section the histology of arterio-sclerosis is critically examined in respect of its bearing on the aetiology of the disease. The clinical section deals with conditions associated with diffuse hyperplastic sclerosis and their inter-relation, namely, raised blood-pressure, cardiac hypertrophy, cerebral haemorrhage, and chronic renal disease. This aspect of the subject being of vast dimensions is considered only from one point of view. Thus, the observations recorded in the pathological section having led to the conclusion that the underlying process in the production of arterio-sclerosis is one of active inflammation, cardiac hypertrophy is only discussed in so far as it provides evidence as to the nature of the aetiological factor whose activity is responsible for active inflammatory reaction in arterial walls. Similarly, in dealing with the subject of chronic nephritis the simplest explanation of the histological picture has been accepted; it has been assumed that where signs of active inflammation are present they are part of the primary disease and not the result of secondary infection. It is obvious that this explanation is not necessarily valid; at the same time it leaves the ground clear for the demonstration of an alternative hypothesis, and provides additional evidence in support of the view that the process underlying the production of arterio-sclerosis is one of active inflammation.

Definition of arterio-sclerosis. Neither Sir Clifford Allbutt (2), Aschoff (3), nor Jores (4) attempt a concise definition of arterio-sclerosis. Sir Clifford Allbutt, for instance, finds a distinction between atheroma and arterio-sclerosis to the extent that the latter includes the former, and he summarizes his views on nomenclature in accepting the term 'athero-sclerosis'. Aschoff attaches importance to sub-endothelial proliferation; hypertrophy is distinguished from sclerosis by the

fact that the former results from proliferation of the elastic fibres in Jores's hyperplastic layer, whereas in the latter the subendothelial layer of the intima is chiefly concerned in the proliferative process. Jores excludes frank inflammatory changes from inclusion under the term arterio-sclerosis, though he recognizes that it is a difficult matter histologically to make a hard and fast distinction. Some authors have attempted to approach the subject of definition by the exclusion from arterio-sclerosis of known forms of arterial disease such as syphilitic disease, but this method of definition will be unsatisfactory until there is a clear idea of the underlying processes whose activity causes the disease. A definition of arterio-sclerosis must avoid reference to any supposed underlying process or aetiological factor. Syphilitic arterial disease demands inclusion, endarteritis cannot be excluded. In the second place the term arterio-sclerosis has equally a clinical and pathological significance, hence it follows that a definition of arterio-sclerosis must include both clinical and pathological aspects of the disease. For this purpose the adjective ' thickness ' is convenient, for it describes a quality that can be equally appreciated by the senses of touch and sight; within certain limits an artery may be felt to be thickened by palpation (say of the radial artery under the skin) as readily as it may be seen to be thickened in cross-section under the microscope. Increased thickness of the adventitia, however, cannot be distinguished from periadventitial fibrosis; increased thickness of the media may result from pure hypertrophy and is a variable factor in any particular part of an artery, for it varies in relation to previous or subsequent offshoots from the artery, in relation to physiological requirements of the part supplied, and in relation to the degree of muscle tone present. We are thus left with the intima, and we find in this coat a certain degree of thickness normal for the artery under examination and varying little within physiological limits so long as due allowance is made for age. In the second place the presence of some form of protein degeneration, of which fatty degeneration is the characteristic form, is almost constantly present in some part of the artery or arterial tree. In this communication, then, *arterio-sclerosis is used to describe an abnormal degree of intimal thickening or the presence of some form of protein degeneration in the vessel wall.* The degree of thickening may be determined by palpation or inspection, and is thus of use in both a clinical and pathological sense; the presence or absence of fatty degeneration depends necessarily on pathological examination. Arterio-sclerosis is defined in the same sense independently by Osler (5) and Ch. Thorel (6), and there is no other definition of arterio-sclerosis on which any two authors are in agreement.

1. The Pathology of Diffuse Hyperplastic Sclerosis.

A. *Material and Method of its Examination.*

The material for histological examination was taken from a hundred post-mortem examinations made at St. Bartholomew's Hospital, to which are added some twenty specimens of tissue removed at operation. The histological observations have been correlated with the macroscopic post-mortem findings and with the clinical notes of the patient's condition before death. The main object in view being a study of diffuse hyperplastic sclerosis, which has a special incidence on the smaller arteries and arterioles, the intimate vasculature of organs has been throughout of chief interest. Several (four to twelve) organs have been taken from a single case with the object of determining the incidence of the arterial lesion in the different organs; specimens of the larger arteries have also been examined microscopically. In routine post-mortem work disease of the intimate vasculature of organs is liable to escape observation; in order, therefore, to observe its occurrence in expected as well as in unexpected conditions a large variety of cases have been examined, including tissues obviously normal and diseases and ages at which diffuse hyperplastic sclerosis could not be expected to be present.

Material taken from the post-mortem room was fixed for twenty-four hours in 5 per cent. Formol-Müller and then transferred to Müller's solution for several days, generally a week or more. It was then washed in running water for twenty-four hours and embedded in gelatin according to J. F. Gaskell's method (18).[1] After fixing the gelatin-embedded tissues in formalin vapour for two or three days, the tissues were cut on a freezing microtome. As a routine, two specimens were prepared from every tissue taken for examination; the one stained in Sudan III and acid haemalum was mounted in glycerin-gelatin, the other stained in acid haemalum and Van Gieson's stain, after clearing in carbol-xylol, was mounted in Canada balsam. Some sections have been stained by other dyes, such as methyl violet for amyloid disease, silver nitrate for calcification, and Weigert's stain for elastic tissue. In many cases several sections have been cut from one organ; in others several parts of one organ have been examined. Three blocks have been cut in serial section in order to examine the extent of the lesion along the length of affected vessels. The vascular lesion is focal in its distribution through the arterial tree, and large blocks of tissue were therefore taken, and all specimens in which the lesion was slight or absent were searched methodically, using a mechanical stage, before the lesion was pronounced to be definitely absent. Of the sections examined, 1,800 were preserved, and the observations made in this communication are based on the examination of these sections.

Further, the medical post-mortem records of the hospital for the past twenty years have been abstracted in so far as they bear on this subject, and the

[1] Gaskell's method has important advantages in that the tissues are not heated above 37° C., nor brought in contact with a fat solvent in the course of their preparation.

statistics thus obtained have been summarized in graphs and tables. Evidence obtained in this way serves to balance deductions from single cases examined in detail.

B. *Histology and Incidence of Diffuse Hyperplastic Sclerosis.*

This variety of arterio-sclerosis mainly affects the smaller arteries and arterioles throughout the body, though in very unequal degree. Some organs tend to escape altogether, though the intimate vasculature of others is severely affected, while within an organ some arterioles may show the lesion in an advanced stage and others remain normal. The kidney is the best organ in which to study the nature of the vascular change, because the lesion is often well marked in the renal vessels, and there are in general more small arteries to be seen in any microscopical section of kidney tissue than in any similar preparation of other tissue.

The following description is taken from sections of a kidney of a man aged 47, a painter by trade, who died of cerebral haemorrhage and 'chronic interstitial nephritis'; also from serial sections of a man aged 76, who died of cerebral haemorrhage due to rupture of an aneurysm in the left anterior cerebral artery. In the first case there was no evidence of syphilis, and the Wassermann reaction was negative; in the second case, the condition of the ascending aorta suggested syphilitic mesaortitis.

(i) *Description of the lesion.* The main features of the arterial change are a fatty degeneration in the intima of the arterioles—the vasa afferentia—together with a hyperplasia of the arteries from which the arterioles spring.

To take the arterioles first, the first change appears to be a hyaline swelling of the intima, which is almost uniform in the length of an arteriole traced from the degenerated glomerulus which it supplies to the interlobular artery from which it arises. In a presumably more advanced state this hyaline degeneration gives place to a fatty degeneration which is less uniform in its incidence on the length of the arteriole. In some parts of the arteriole the intimal swelling is hyaline, while in other parts it has undergone fatty degeneration of varying degree and varying reaction to Sudan III stain. Thus, in some sections of the same arteriole the fat is stained a crimson red; 30 to 60 μ distant it may be yellow or any variation of colour between red and yellow, to become red again or only faintly fat-staining in later sections of the series. The muscular coat in the pure condition does not show any hyaline or fatty change, while there is frequently an increase of fibrous tissue around the vessel due to an increase in the adventitial layer or due to a perivascular fibrosis. The media is thicker than normal, as a result of hypertrophy, and the muscle-cells stand out distinctly in circular rings two or three cells thick. The arteriole, as a whole, is markedly tortuous; its lumen is much narrowed or is entirely obliterated by the intimal thickening. The affected arterioles, seen in cross-section stained with acid haemalum and Sudan III, stand out characteristically from the surrounding tissue as small, circular, bright-

red dots, in the centre of which, under high power, two or three endothelial cells are sometimes seen clumped together in the form of a rosette; surrounding the spot of fat is a thickened, but otherwise normal, media of two to four cells' thickness. The obliteration of the lumen is probably often only apparent. McCordick has called attention to the fact that the cells of the media contract in death, and this fact is very obvious in the examination of arteries of larger size where the presence of an internal elastic lamina and its undulating form give an approximate idea of the extent of this medial contraction. Other evidence on the same point is supplied by an examination of the arterioles of the spleen. In the normal organ, where there is every reason to believe that the vessels are also normal, the endothelial lining of the splenic arterioles is commonly swollen and the lumen extremely small or almost occluded. Since this appearance is found under normal conditions the occlusion of the lumen can only be apparent and due to contraction of the cells of the media in death. In judging, therefore, the degree of occlusion of the finer arteries and arterioles as seen in histological preparations prepared by Gaskell's method, it is necessary to bear this point in mind, for, with the raised blood-pressure commonly met with in these cases, together with a certain degree of muscular relaxation of the media, an apparently occluded lumen may be sufficiently patent during life.

In contrast to the degenerative changes found in the arterioles there is a hyperplasia without fatty degeneration in the arteries from which they arise. This change is an exaggeration of the arterial changes that Jores has described as occurring in the larger arteries in the active period of growth. There is a proliferation of the specialized tissue-cells that form the arterial wall, and especially of the intimal coat. The internal elastic lamina is thickened and as many as four or even five laminae of elastic tissue are split off from its inner aspect, while in other arteries (as in that drawn in Fig. 1, Plate 3), instead of the formation of new layers of elastic tissue, there is a diffuse infiltration of the thickened intima with fine elastic fibrils that have in general a circular arrangement. The main mass of intimal thickening consists of a hyaline material in which scattered cells are visible. The nuclei of these cells stain distinctly and are not degenerate in appearance. They are frequently elongated or spindle-shaped, particularly in the innermost part of the thickened intima, where they may sometimes be seen in a regular circular arrangement, forming concentric rings of which the intact endothelium forms the innermost layer. In the deeper layers there are generally fewer nuclei, and those present are more often circular or polygonal rather than elongated and spindle-shaped. In some cases the endothelial cells are collected in a rosette in the centre of the nearly obliterated artery, and they may be rich in plasm and occasionally elongated radially. It is not clear to what extent the hyaline matrix, which often forms the main part of the intimal thickening of these arteries, is a degenerative change. It may be identical with that which occurs in the arterioles before the fatty change occurs. On the other hand, it would seem to be different, because fatty degeneration is less prone to occur in the arteries of this particular size; the nuclei embedded in the hyaline matrix

stain well with haemalum, the lesion is a productive one as shown by the increase of elastic tissue, and finally the change from fatty degeneration in the arteriole to the productive intimal thickening of the artery from which the arteriole arises is abrupt.[2] The fatty arteriole change ceases abruptly at its origin from the artery and does not extend into the intima of the artery as does the muddy water of a brook into the river it feeds. Sir Clifford Allbutt (2) quotes a similar observation made by Jores of 'arterio-sclerosis of the vas afferens only "*sharp at its offshoot*" from the interlobulare'.

In addition to the intimal hyperplasia, there is medial hypertrophy of the arterial wall. There are typically no degenerative changes in the media nor evidence of fibrosis. In some cases there is obvious adventitial thickening, either due to an increase in the fibrous tissue of the adventitia or of the peri-adventitial connective tissue.

As regards the artery as a whole, being on a larger scale than the arterioles, it is difficult to demonstrate in serial sections the variations in the intimal thickening in the length of the vessel. Judging from arteries that chance to be cut in longitudinal section, it is concluded that the intimal thickening is very uniform in the length of the vessel, and the thickening is certainly uniform in the circumference of the vessel. These tiny arteries, like the arterioles and larger arteries of the intimate vasculature, run a tortuous course. The intimal hyperplasia leads to a marked narrowing of the lumen. The lumen is quite commonly reduced to one-half its normal diameter, and it is sometimes quite occluded without there being thrombosis or other morbid condition than the hyperplasia already described. It is concluded that the occlusion in these cases is apparent—a post-mortem phenomenon.

The larger arteries of the intimate vasculature show the same condition to a lesser degree. There is the same intimal hyperplasia and medial hypertrophy without degenerative change.

In the particular specimens from which the description is taken the renal artery was not examined. A corresponding change would have been found in its walls, except that there might have been early fatty degeneration in the subintimal coat. The internal elastic lamina is frequently the first tissue in the intima to show this change, a fact noted by Andrewes. It is characteristic of the pathological change in this variety of arterio-sclerosis that the whole circumference of the vessel tends to be uniformly involved.

(ii) *Variations from the typical lesion.* In less advanced cases, the interlobular arteries may not show any change though the section reveals a few arterioles that have undergone the typical change described above. If the arteriole change is the primary condition this absence of change in the parent trunks may be explained on the assumption that the arteriole involvement is too partial to have had any effect on the larger arteries. On the other hand, it is not

[2] The most marked example of hyaline swelling of the intima is to be seen in the arteries of the puerperal uterus, and in these the underlying process is one of involution or atrophy rather than degeneration.

uncommon to find a marked intimal hyperplasia of the interlobular arteries with little involvement of the arterioles, and in some cases no obliterated arteriole has been found in a section that showed well-marked hyperplasia of the intima of parent vessels.

Sometimes in the kidney, and more often in the spleen, fatty degeneration of the hyperplastic intima of the second size arteries is found. Fig. 2, Plate 3, shows this change in a marked form. The illustration shows the condition better than a description, and it will be seen on careful examination of the drawing that the area of fatty degeneration in fact consists of endothelial-like cells, whose original form and faint remnant of nuclei are still in part visible in spite of the fatty change.

The media may be thinned instead of hypertrophied, and may show evidence of fatty degeneration in organs taken from subjects of more than 50 years of age. It is in part due to the introduction of the senile form of arterio-sclerosis as a complicating factor in the picture. It is in other cases obviously due to a toxic condition of the surrounding tissues of marked degree, as in Case No. 21, where there was marked tuberculous disease.

Where intimal hyperplasia occurs in the senile form of arterio-sclerosis, it is less regular in form and less marked in degree than it is in diffuse hyperplastic sclerosis. The intimal thickening is rarely uniformly disposed in the circumference of the vessel, appearing rather as a nodular thickening on one side of the wall, which nodular thickening may be related to an underlying medial degeneration.

(iii) *Distribution of the lesion within an organ.* The distribution of the arteriole lesion in the intimate vasculature of an organ is extremely partial, nor is it clear what factor determines the affection of some arterioles while others completely escape. From an examination of a long series of sections of two kidneys cut in serial section I have been able to confirm Gaskell's observation that the degenerated arteriole is the vas afferens of a degenerate glomerulus. The initial pathological change appears to be in the glomerular tuft and not in the vas afferens. In the other organs of the body the same capricious incidence occurs. The splenic arterioles suffer more uniformly than do the arterioles of other organs, but even in this organ some arterioles are completely sclerosed, while others are normal. In the brain, pancreas, liver, and lungs, fewer arterioles appear in any one section of tissue, but, allowing for this fact, the incidence of the change appears even more strikingly capricious in its distribution.

In some cases so few arterioles are affected that the lesion may escape observation unless carefully looked for. It has been the practice to take large pieces of tissues for examination and to search them carefully with the use of a mechanical stage under the low power. With this method, as a result of searching many sections with a negative result, I have come to the conclusion that the arteriole lesion is probably not present in the block of material taken if it is not found in the first two sections examined. The arteriole lesion may be expected to be present when the arterioles show medial hypertrophy or where there is an intimal hyperplasia of the smaller arteries from which they arise.

When either of these two conditions are observed a more careful search is required before making a negative report. Hyperplastic changes in the second and third size arteries are less common and less marked in other organs than the kidney.

(iv) *Distribution of the sclerosis in the several organs.* For convenience of description the word 'arteriole' is used for the smallest arterial twigs whose media are of two or three muscle cells in thickness. They are typically of the size of vasa afferentia. Second size arteries are of the size of interlobular arteries and their medial coats are 4 to 8 muscle cells in thickness. Third size arteries are of the size of branches of the renal artery. These phrases are not used in a very exact sense, and in comparison a fourth size artery would be of the size of the radial or basilar artery.

Kidney. The vascular lesion will be discussed separately in detail in the section dealing with chronic nephritis. Diffuse hyperplastic sclerosis is more common in the kidney than in any other organ. Sixty-two cases have been examined. Of these the lesion was found in greater or lesser degree in twenty-seven cases, whereas it was present in the spleen vasculature in twenty-three of these cases. The difference in incidence of the lesion as between the kidney and spleen is not great. The intimal hyperplasia affecting the interlobular arteries and larger arteries of the intimate vasculature of the kidney is more marked in this organ than in any other. It is, in fact, often so prominent a feature of the histological picture as to suggest to those less familiar with the lesion that the aetiological factor is syphilis. It is, therefore, emphasized tha the intimal thickening, even when of marked degree and almost obliterating the arterial lumen, is not indicative of syphilis, even though, as will be seen later, syphilis cannot be excluded in some cases. Fatty degeneration of the hyperplastic intimal layer of the second and third size arteries is not usual; when present the specimen is generally found to be from a body over fifty-five years of age.

Spleen. The arterioles and smallest arteries, when the tissue is embedded in gelatin and cut frozen, differ in appearance from vessels of similar size in other organs, in the smallness of their lumen. The condition is due in part to the endothelium of the arterioles in the spleen being more cellular than elsewhere, or to a pathological swelling which occurs normally and rapidly after death; it results in part from contraction of the media in death. In the case, therefore, of the splenic arterioles, hyaline swelling of the intima is not in itself sufficient evidence of a pathological change, and a search must be made for the presence of fatty degeneration. Fifty-eight cases have been examined, and the typical condition of diffuse hyperplastic sclerosis, in so far as the arterioles are concerned, has been present in twenty-seven cases to a greater or lesser degree. The lesion does not differ in its histology from that found in the kidney, except that there is a tendency to fatty degeneration of the hyperplastic intima in the smaller arteries, a tendency which is less obvious in the renal arteries. In the kidney the fatty degeneration of the intima is generally limited to the arterioles, and

even the smaller arteries do not commonly show this change. The intimal thickening of the smaller arteries is a less obvious feature in the spleen than in the kidney. Slight and early stages of the lesion have been found in the spleen while absent from other organs in the body. In these cases the complete lesion is not developed, and the lesion consists of a fatty degeneration in the swollen intima of occasional arterioles without coincident intimal proliferation in arterial twigs or second size arteries.

The presence or absence of diffuse hyperplastic sclerosis in the intimate vasculature of the spleen is a criterion of its general incidence in the body as a whole. My observations show that this vascular lesion is more frequently and constantly present in the spleen and kidney than in any other organ. The lesion has not been found elsewhere in the body when absent simultaneously from the kidney and spleen. The renal vascular lesion is too closely associated with chronic kidney disease to permit a fair deduction to be made as to the presence of diffuse hyperplastic sclerosis elsewhere from the fact of its presence in the kidney, hence the spleen is the most important single organ in the body for the post-mortem diagnostic observation of the presence or absence of this vascular lesion; the extent, also, to which the intimate vasculature of the spleen is affected gives some indication of the severity of the lesion elsewhere. The spleen may be the only organ affected.

Brain. Diffuse hyperplastic sclerosis in this region, particularly when the arterioles supplying the medulla oblongata are involved, must be of exceptional importance, since the arteries of the brain are as definitely 'end-arteries' without collateral anastomosis as are the afferent arterioles to renal glomeruli. If the lesion leads to an obliteration of the arteriole lumen the effect must be greater (on the tissue supplied) in the case of the medulla than in the kidney, because the glomerular function is reduplicated in structure many thousands of times, whereas the medullary nerve-centres are single and essential to life.

Having in mind the pressor effect of medullary anaemia (Leonard Hill), I expected to find an obliterative intimal thickening in the medullary arterioles in cases of raised blood-pressure, on the hypothesis that such obliterative change would result in a medullary anaemia comparable to that produced by external pressure.

For the study of arterial change in the medulla, pons, and mid-brain, it is necessary to remove the tissue for examination intact with its covering meninges, since it is in the vessels of the pia mater that the arterial change is most frequently seen. Diffuse hyperplastic sclerosis as seen in the brain is comparable to that which occurs elsewhere in the body, only that the intimal hyperplasia in the second and third size arteries is not marked.

No case has been observed in which this intimal hyperplasia has been the prominent feature that it so often is in the kidney and spleen. The fatty obliteration of the lumen is sometimes advanced, leading to complete blocking of the lumen of arterioles. The lesion is not generally widespread, and in a single section is to be found in only one or two arterioles, the remainder

showing perhaps slight degrees of the lesion or more generally having a normal appearance. Since special interest attaches to the arteries of the brain, several parts of the brain-stem, medulla, pons, and mid-brain were generally examined.

The lesion was found in fourteen cases of thirty-five brains examined. In all cases in which the lesion was present in the brain it was also evident, and to a greater extent, in both kidneys and spleen. The evidence, therefore, from this series does not support the thesis advanced by Aschoff that the arterial lesion falls with greater weight on the intimate vasculature of the brain in some cases, and on the intimate vasculature of the kidney in other cases.

I am not aware that Aschoff has made a comparative examination of the intimate vasculature of organs in any series of cases such as forms the basis of the present research. His conclusion is possibly based, in the first place, on the clinical fact that, in some cases in which diffuse hyperplastic sclerosis is the vascular lesion, death occurs from cerebral haemorrhage, while in another group of cases death results from uraemia; and in the second place, on the gross morbid anatomy fact that nodular sclerosis may be advanced in the larger arteries of the base of the brain and branches of the middle cerebral artery while other arteries in the body show little or no evidence of this lesion. If this assumption of the grounds on which Aschoff bases his observations is correct, it is easy to understand the apparent discrepancy between his statement and the observations here recorded. Nodular sclerosis of the arteries of the base of the brain is by no means equivalent to diffuse hyperplastic sclerosis affecting the intimate vasculature of the brain, nor is cerebral haemorrhage by any means equivalent to this arterial lesion.

In short, diffuse hyperplastic sclerosis was rarely a marked lesion in the brain in this series of cases; and though it was actually found in fourteen of thirty-five cases examined, it was generally only present in a few arterioles. Further, since the specimens were taken from selected cases, the proportion of positive findings gives an exaggerated impression of its prevalence.

Liver. Forty-six cases have been examined, in thirteen of which fatty obliteration of arterioles was found. As in the case of the brain, the lesion is extremely capricious, affecting often only an occasional arteriole, while the intimal hyperplasia of second and third size arteries is again, though evident, no prominent feature. In general, diffuse hyperplastic sclerosis is an unimportant lesion in the liver. It has not been found in several cases that showed early cirrhosis, nor was it present in the case of a child aged 16 who died of Banti's disease with advanced cirrhosis of the liver.

Pancreas. This organ has been examined in twenty-one cases, six of which showed diffuse hyperplastic sclerosis. The best-marked example was found in the case of a man aged 67 who died of cerebral haemorrhage, with a heart weighing 24½ ozs. In this case the lesion was well marked in the kidney, spleen, and brain, and was also present in the liver and suprarenal gland, though absent in the heart, stomach, lung, and skeletal muscle.

Alimentary tract. The stomach has been examined in seventeen cases, the

large or small intestine (or both) in eight cases, and in no single case has diffuse hyperplastic sclerosis in the intimate vasculature of these organs been found. Though the number of cases examined is relatively few, it is noteworthy that the lesion was not found in a single case. If this arterial lesion is in any way a cause of high blood-pressure and cardiac hypertrophy, it is evident that it is not in its incidence on the intimate vasculature of the alimentary tract that the explanation for the association is to be looked for. This observation supports other evidence that has been brought forward to controvert the thesis put forward by Hasenfeld and Hirsch that splanchnic arterio-sclerosis is a cause of raised blood-pressure. It may be noted in passing that Marchand has also brought forward evidence against the splanchnic sclerosis theory of raised blood-pressure, and Sir Clifford Allbutt (*loc. cit.*, p. 332) dismisses it finally as of no account.

Lung. Twenty-seven cases have been examined. The complete lesion was not found in any case, but in one case there was marked intimal hyperplasia of the second and third size branches of the pulmonary artery. It is a well-known fact that arterio-sclerosis of the intimate vasculature of the lung is rare except as a local condition associated with local fibrosis, as in chronic tuberculous disease. The absence of the lesion in the present series of cases is therefore to be expected.

Suprarenals. Fifteen cases have been examined, in two of which the typical lesion was present. In two other cases there was intimal thickening of second size arteries without fatty obliteration of arterioles.

The thyroid, pituitary, thymus, ovaries, prostate, skin, bladder, and uterus have been examined in a few cases, but their number is too few to form the basis of observation. It may be mentioned in passing that in one case, a female, aged 53, who died of uraemia due to polycystic kidneys, the typical lesion was present in the ovaries. I have not examined sufficient controls to attach importance to this observation.

Heart. The following table gives a summary of the cases in which the intimate vasculature was examined microscopically. No general reference is made to the coronary arteries or their main branches; where a vascular lesion is mentioned, it refers only to the intimate vasculature—that is, to arteries of a size that correspond to that of the interlobular arteries of the kidneys, or to vessels of a smallar size.

m f = fatty degeneration in the media.
sl m f = slight fatty degeneration in the media.
c f = fatty degeneration in slightly thickened intima; in no case was there marked thickening of the intima.
c = intimal thickening.
n l = normal.

Details of 52 Cases.

Case.	Age.	Heart Arteries.	Cause of Death.
1 a	43	n l	Bronchitis, heart failure ; seq. fractured ribs
7	64	m f	Pneumonia
8	51	n l	Heart disease, aortitis
9	43	n l	Influenza
10	47	n l	Cerebral haemorrhage
11	35	n l	T. B. pulmonum
12	44	n l	Perinephric abscess, septicaemia
13	44	n l	Haematemesis, gastric ulcer
14	43	n l	Cerebral haemorrhage
15	36	n l	Diabetes mellitus
16	57	c f m f	Prostatectomy ; ? uraemia
17	68	larger arteries c f	Suprarenal tumour
1	29	n l	Uraemia
2	53	sl m f	Cerebral haemorrhage
3	35	n l	Uraemia
4	39	n l	Uraemia
18	76	m f	Cerebral haemorrhage
19	47	n l	Gangrenous cystitis
20	17	n l	Fractured base
22	76	m f	Arterio-sclerosis
23	45	larger arteries c	Heart failure
24	61	n l	Nephrectomy, uraemia
25	67	m f	Cerebral haemorrhage
26	66	m f	Uraemia following prostatectomy
27	51	n l	Cerebral haemorrhage
28	8	n l	Rheumatic fever
29	46	n l	Uraemia
30	55	n l	Pneumonia
32	86	m f	Cystitis; ? uraemia
33	62	n l	Carcinoma uteri.
34	47	n l	Cerebral haemorrhage.
35	58	c (in one artery)	Intestinal obstruction
37	41	n l	Perinephric abscess
38	62	m f	Carcinoma of stomach
39	31	n l	Suppurative otitis media, septicaemia
41	39	n l	Fractured base
42	27	n l	Malignant endocarditis
43	46	n l	Cerebral haemorrhage
44	53	n l	Polycystic kidneys, uraemia
46	64	n l	Cellulitis of arm, septicaemia
46 b	15	n l	Icterus gravis
49	33	n l	Tied ureter
52	8	n l	Rheumatic fever
53	65	n l	Cerebral haemorrhage
55	16	n l	Rheumatic fever, malignant endocarditis
56	63	n l	Uraemia
57	16	n l	Tuberculous kidney
60	38	n l	Pneumonia
61	36	n l	Cerebral haemorrhage
63	16	n l	Banti's disease
64	83	n l	Prostatectomy ; ? uraemia
65	52	n l	Heart failure

Diffuse hyperplastic sclerosis, affecting the intimate vasculature of the heart, was not found in any specimen examined. As regards the age of the cases

included in the series, it will be seen that there are twenty-two above the age of 50 years, of which ten are over 60 years, two over 70 years, and two over 80 years. In eleven cases there was marked diffuse hyperplastic sclerosis elsewhere in the body, and in several there was advanced arterio-sclerosis of the coronary arteries.

No lesion of capillaries in the heart-muscle was observed. The only lesion found in the intimate vasculature of the heart was a slight degree of fatty degeneration in the media of the finer arteries in cases aged respectively 53, 64, 57, 68, 76, 76, 67, 66, 86, and 62 years. The age incidence of the lesion, its nature, a fatty degeneration, and its situation in the media are evidence of its being of the senile type of arterio-sclerosis—that is to say, of fifteen cases whose age at death was more than 55 years, no less than nine showed evidence of senile arterio-sclerosis in the intimate vasculature of the heart. No case under 50 showed this lesion.

In one case there was a slight fatty degeneration in the intima, in addition to the medial change, and in three cases there was some intimal thickening in arteries of larger size. There is one exception to the general statements made above, in that a single arteriole in one heart showed intimal hyperplasia due to proliferation of the endothelium without evidence of degeneration. In the absence of fatty obliteration of the arteriole lumen this lesion is excluded from the typical condition described as diffuse hyperplastic sclerosis. It may be, however, that it rightly belongs to this group of arterio-sclerosis. These observations confirm Jores's statement that diffuse hyperplastic sclerosis is uncommon in the intimate vasculature of the heart.

Skeletal muscle. Thirty-one cases were examined, and in only one of these was there any change in the intimate vasculature. The typical lesion was not found in any specimen. The specimens were in general selected from those cases in which arterial change was thought most likely to occur, while there are included in the series one case of senile gangrene, two cases of diabetic gangrene, and one case of thrombo-angiitis obliterans. These sections were made from the soleus muscle, which itself showed evidence of fatty degeneration in the senile and diabetic gangrene cases. Only one specimen showed a vascular change. In this specimen one arteriole showed an irregular thickening of the intima with slight fatty degeneration, while a second, cut in longitudinal section, showed a little fat stain in the intima or media. This patient died of cerebral haemorrhage and there was some evidence of the vascular lesion being syphilitic.

C. *Local Hyperplastic Sclerosis and Unit Processes in Arterial Disease.*

The aetiology of arterio-sclerosis is still a matter of speculation. The importance of certain factors in its production, such as syphilis, lead, and tobacco, are recognized, and there is some evidence that raised blood-pressure may be a determining factor. The evidence as regards these factors being

anything more than contributory causes of diffuse hyperplastic sclerosis is not indisputable. Yet the question as to whether this or that factor plays a part in the production of arterio-sclerosis is a problem of secondary interest so long as the nature of the underlying process is undetermined. Broadly considered, there are only four possible and fundamental underlying processes, namely:

Physiological: (*a*) Growth.
(*b*) Involution.
Pathological: (*c*) Inflammation.
(*d*) Degeneration.

The foregoing study of diffuse hyperplastic sclerosis shows it to be a composite lesion. The occurrence of fatty degeneration in the intima is evidence of a protein degeneration attributable to the toxic action of a *materies morbi*; the intimal proliferation and medial hypertrophy may be explained in terms of growth or inflammation, and where intimal thickening occurs alone it may be evidence of involution.

In the following paragraphs these several processes will be reviewed seriatim in an attempt to analyse the composite lesion diffuse hyperplastic sclerosis in terms of one or more of the unit processes; at the same time certain forms of local hyperplastic sclerosis will furnish pure examples of the arterial change that results from the activity of one or other of the unit processes.

Before passing on to this subject it may be mentioned that the blood-supply of arterial walls is not fully known. The blood in their lumen no doubt nourishes the endothelium; it is probable that it does not supply any other part of the arterial wall, since complete thrombosis is not followed by any change other than that of involution. The first part of the aorta is supplied by vasa vasorum. Sir Frederick Andrewes has told me that he has not found vasa vasorum in other arteries, nor have I found a vas vasorum in any arteries that I have examined excepting the aorta. Though somewhat paradoxical, *it is reasonable on present evidence to regard arterial walls as relatively avascular tissues*, and if this is so it must materially modify any process of active inflammation that tends to occur in them.

(i) *Physiological process.* (a) *Growth.* Jores has made a particular study of the changes in the intima of the aorta in growth. At birth the intima consists of an endothelial lining resting on a minimal fibrous connective tissue stroma which separates it from a single sheath of elastic tissue, the internal elastic membrane. During the first two years of life there occurs a thickening and splitting of the internal elastic membrane into two layers, the outer and inner elastic laminae; the latter splits again into two layers called the elastic boundary lamella and the elastic boundary stria, between which longitudinal muscle-fibres are developed forming the musculo-elastic layer of Jores. There is coincidentally a slight thickening of the fibrous connective tissue on which the endothelium rests.

The similarity of these changes to those seen in the intima in diffuse hyperplastic sclerosis has led Jores to explain the latter in terms of physiological

response of the arterial wall to the increased blood-pressure with which the condition is generally associated—that is to say, in terms of Jores's hypothesis, that the unit process underlying arterio-sclerosis is that of growth.

This interpretation may have some truth in it, but that it is not the whole explanation is obvious from the fact that a marked degree of diffuse hyperplastic sclerosis may occur without marked increase in the blood-pressure, as judged by the degree of cardiac hypertrophy *post mortem* (*vide* section dealing with cardiac hypertrophy). Further, this interpretation does not explain the localization of the lesion of diffuse hyperplastic sclerosis in the several organs of the body. Thirdly, it is to be observed that the interpretation rests largely on the histological appearance of the thickened intima, and, as will be shown in the succeeding paragraphs, a comparable histological picture may result from other unit processes than that of growth; there is no critical histological difference in structure between diffuse and localized hyperplastic sclerosis, and therefore, in so far as microscopical changes in the structure of the intima form the basis of argument on which this interpretation depends, localized hyperplastic sclerosis should equally result from intimal reaction to raised blood-pressure. Lastly, fatty degeneration is a characteristic feature of arterio-sclerosis, and it does not occur in the process of growth.

(b) *Involution.* Thoma's name, more than any other, is associated with the interpretation of arterio-sclerosis in terms of involution (12). His theory of arterio-sclerosis is not actually stated in terms of involution, but his observations were initially based on the changes in the intima of the umbilical and hypogastric arteries that occur after birth and result in a narrowing of the lumen due to the blood-stream being retarded by their occlusion. The narrowing of the lumen is effected by medial contraction and intimal proliferation, and by the same hypothesis Thoma explains the changes in the arterial wall that result from ligature as well as those changes in the pulmonary artery that are associated with fibrosis and cavitation in the lung. In short, retardation of the blood-stream is the immediate cause of the new formation of connective tissue in the intima of the widened artery, and in these terms Thoma finds an explanation for both local and diffuse hyperplastic sclerosis. Thoma emphasizes another important feature of circulatory change, which involves the recognition of the involution process, when he states that 'it is the organ itself which determines the quantity, the rate of flow, and the presence of the blood flowing through it'. In its further application Thoma's theory involves the principle of a replacement fibrosis, and to this extent introduces the unit process inflammation into the interpretation of arterio-sclerosis; but even in this application of his theory the underlying principle is rather *compensation* than tissue proliferation in direct response to injury —that is, 'replacement fibrosis' rather than 'active inflammatory' reaction. Thoma's views are well reviewed by Ch. Thorel, and Sir Frederick Andrewes (11) has given a critical summary of their present-day significance.

The clearest illustration of physiological involution is seen in the involution of the hypogastric arteries and ductus arteriosus after birth. The progress of

involution in the hypogastric arteries is traced by examination of arteries taken from infants who have died at varying intervals after birth.

The earliest change observable in the hypogastric arteries taken from infants 2 and 3 days old is a subendothelial proliferation at one part of the circumference, leading to slight thickening of the intima; opposite this thickening, at the other end of the section (the artery is flattened), there is the same subendothelial proliferation, and, in addition, a splitting of the internal elastic lamina together with an invasion of the underlying media in its innermost layers by proliferating intimal cells. A case aged 4 months shows a further stage of involution. The lumen is not yet obliterated, but is very small. The section of a hypogastric artery, taken from a case aged 10 months, is reproduced in Fig. 2. The media is still intact; the internal elastic lamina is folded, showing that medial contraction plays a part in obliteration of the lumen; it is also considerably thickened and split in one part of the circumference into two layers. There is a proliferation of the subendothelial tissue, and it is the multiplication of the cells of this tissue, penetrated by new fine elastic fibres, that separates the internal elastic lamina from the underlying media. In the original lumen are three vascular channels. Sections through other parts of the same artery show that one vascular channel is the old lumen, while two are new-formed channels. Other new vascular channels are seen in the media. The great increase in tissue that takes place in involution is rendered striking when comparison is made with sections of hypogastric arteries taken from infants two or three days after birth, in which there is, in the greater part of the circumference, a minimal amount of subendothelial tissue; the endothelium appears to rest directly on the internal elastic lamina, which is a single lamina in contact with the media. At one year and seven months, the same changes in an advanced degree are present; considerable muscular atrophy has taken place, and the whole tissue is shrunken. Similar changes occur in the umbilical vessels.

The main features of involution are contraction of the media, swelling and splitting of the internal elastic lamina, subendothelial proliferation, occurring both within and without the internal elastic lamina, and penetration of new vascular channels. The final stage is ushered in by simple atrophy and increase in the hyaline material in the intimal and medial coats. It is to be noted that there is no small-cell infiltration and *no fatty degeneration in hypogastric artery involution.* These observations confirm the work of past observers, and reference may be made to the work of Pollot, and later Weissmann (13), who studied the involution of the ductus arteriosus.

The arterial change that follows embolism, thrombosis, or ligature may be of the fibrous form—that is, the form in which subendothelial hyperplasia is marked, and little change takes place in the internal elastic lamina apart from the formation of fine elastic fibrils permeating the fibrous mass of the intima. This appearance has led to the classification of the arterial changes that follow embolism, thrombosis, and ligature, under the main heading 'primary intimal

disease' (corresponding to Jores's regenerative connective tissue over-growth), thus involving the assumption that the arterial changes are 'inflammatory' in the broad sense of the word (Andrewes). It is not, however, necessary to strain the interpretation of the word inflammation to include these changes, for they are identical with and are in fact the changes that occur in involution; they are part of a physiological process rather than of a disease. Further, the changes in arterial walls in involution may closely simulate the changes typically occurring in second size arteries in diffuse hyperplastic sclerosis. Sections prepared from a kidney, whose intimate vasculature was normal except in the region of a depressed scar that had resulted from cicatrization of an infarct, showed several second size arteries in the neighbourhood of the scar, afferent arteries to the scarred area. In these arteries there was marked intimal hyperplasia and splitting of the internal elastic lamina into three definite layers. There was no inflammatory reaction in the neighbourhood nor fatty degeneration. The arterial change was similar to that found in the second size arteries of renal sclerosis. It is impossible to interpret the arterial change in terms of the unit process growth; it is in appearance not typical of the changes that result from the activity of the unit process inflammation (such as are recognized by Jores and others); it is in fact pure involution. This specimen, therefore, raises the question as to how far the histological appearances of vascular changes in arterio-sclerosis are capable of explanation in terms of involution. It also emphasizes the new standpoint from which the whole subject is viewed, for it is no longer a matter of first interest as to whether the changes in arterio-sclerosis are primarily intimal or primarily medial; the fundamental inquiry concerns the identification of the underlying unit process and the determination as to its nature, whether it is physiological or pathological, whether it is growth, involulution, inflammation, or degeneration.

Other examples of arterial involution have been looked for in the thymus gland, in the uterus and ovaries. The thymus proved disappointing and no vascular changes were found in this gland. Vascular changes in the ovaries are too complex for the purpose of the present study; those that are found in the puerperal uterus are, however, of interest.

I have had the opportunity of examining a uterus removed by operation twenty-four days after delivery, in the seventh month, of a dead foetus. Abortion was induced on account of bleeding due to a carcinoma of the cervix. The organ was in a condition of subinvolution. Its vessels showed the early stages of involution in the presence of cellular proliferation of the subendothelial layer and splitting of the internal elastic lamina. There was no fatty degeneration. Goodall and others state that fatty degeneration occurs in the muscle-fibres of the media of the arteries in the body of the puerperal uterus. These observations are based on the examination of pathological material and are not evidence of fatty degeneration occurring in normal arterial involution. So far as my observations go, fatty degeneration does not occur in arterial involution any more than it does in growth. The presence of fatty degeneration in an arterial

wall is, in my opinion, conclusive evidence of the activity of a pathological process. In connexion with the internal elastic lamina proliferation observed in uterine involution it is noted that the growth factor may be involved, since there is evidence that the uterus renews its vessels after each pregnancy. This possibility does not affect the present argument, since the observations on uterine involution are introduced in support of the thesis that fatty degeneration is no part of the physiological process involution.

(ii) *Pathological process.* (c) *Inflammation.* We turn now to the consideration of unit pathological processes in arterial change. While Jores's name is closely associated with the importance of the *Growth* process, and Thoma's name with the importance of the *Involution* process in arterio-sclerosis, Virchow stands out as the champion of the view that arterio-sclerosis is an *Inflammatory process.*

Virchow introduced the term Endarteritis Chronica Deformans for arterio-sclerosis, and he used the word to describe a parenchymatous inflammation of the intima with active proliferation of the cellular elements and simultaneous metamorphosis of the intercellular substance (quoted from Ch. Thorel (15), p. 1003).

Jores recognizes the activity of an inflammatory process in many conditions which are included in this thesis under the term arterio-sclerosis, such as the intimal thickening that follows ligature, embolism, and thrombosis; the intimal thickening in hypogastric artery and ductus arteriosus involution; the intimal proliferation in syphilitic and tuberculous endarteritis and the changes that occur in arterial walls in the neighbourhood of abscesses and tumours. Since, however, proliferation of the internal elastic lamina is a characteristic feature of diffuse hyperplastic sclerosis and characteristically absent in many specimens of pure inflammation, Jores excludes from inclusion under the term of arterio-sclerosis arterial changes that are clearly inflammatory. Like Thoma, however, Jores introduces the inflammatory process into his conception of arterio-sclerosis in recognizing fibrous connective tissue proliferation secondary to local or diffuse fatty degeneration in the hyperplastic intima or in the underlying media. Inflammatory change is thus a secondary phenomenon and not a primary process in the development of arterio-sclerosis according to Jores. (For a summary of Jores's views, *vide* Ch. Thorel, *Lubarsch-Ostertag*, 1903, i. 1015.)

Acute inflammation. Acute arteritis occurs in two forms; the common form is a small-cell infiltration of all coats without any definite thickening of the intima. Since arterio-sclerosis is practically defined in terms of intimal thickening, this form of arteritis is not included under the term arterio-sclerosis. Further, small-cell infiltration is in general conspicuous by its absence in arterio-sclerosis.

Rarely, in my experience, there occurs an acute endarteritis in which the inflammatory change is limited to the intima and is characterized by endothelial proliferation, perhaps also by subendothelial proliferation. In sections prepared from the heart of a patient who died of rheumatic fever with marked pericarditis I found in the thickened pericardium several arterioles whose lumen was blocked

with proliferated endothelial cells. The cells are long and narrow with oval nuclei, and are described as tongue-shaped cells because they have the appearance of being attached at their base and free towards the lumen ; there is no evidence of degeneration in them. In examining arteries that show intimal hyperplasia it is difficult to decide whether the cellular proliferation is or is not in part due to proliferation of the endothelial cells, or whether it results entirely from proliferation of the subendothelial cells of the intima. It might thus be argued that the endothelial proliferation in this specimen is capable of interpretation in terms of an 'involution' phenomenon, but the very uncommon and characteristic appearance of the cells that block the lumen, together with the fact that one arteriole in the kidney showed a similar, though less pronounced change, decides the question of its being an inflammatory change. The same change has been found in three other specimens.

The second case is that of a patient who died of icterus gravis, and the small arteries of the liver showed acute endarteritis. One of the arteries, showing this characteristic picture of acute endarteritis, is drawn in Fig. 3, Plate 4. The drawing shows the condition so perfectly that further description is unnecessary; it is to be noted that the internal elastic lamina is intact.

The third specimen of acute endarteritis is drawn in Fig. 4, Plate 5, and is taken from a section of a fibrolipoma which will be referred to later.

The fourth specimen is the most perfect example of acute endarteritis. It is present in a tuberculous pyonephrosis, and the same section shows several arteries in which this type of inflammatory change is present. There is no change in the media. In the subendothelial layer of the intima there is marked proliferation consisting of several layers of elastic tissue split off from the internal elastic lamina, a hyaline matrix, and a few connective tissue cells. Within this layer are two concentric rings of flattened endothelial cells, while spreading radially into the lumen are the tongue-shaped cells, so called because they have the appearance of being free at their extremity towards the lumen. The lumen is much narrowed by the intimal proliferation.

Chronic inflammation. In the type of subacute or chronic arteritis we are on familiar ground. It occurs commonly in syphilis and tubercle as an intimal thickening due to subendothelial proliferation. It is known as syphilitic or tuberculous endarteritis. A specimen of syphilitic endarteritis affecting a cerebral vessel was kindly lent me by Sir Frederick Andrewes and is drawn in Fig. 5, Plate 5. It is identical with a specimen, in Dr. Thursfield's collection, of tuberculous endarteritis taken from a case of tuberculous meningitis. There is nothing histologically distinctive in syphilitic endarteritis, nor is it even more extreme than the similar change seen in ordinary sclerosis. The intimal thickening in diffuse hyperplastic sclerosis may progress to almost complete obliteration of the lumen. In fact, neither in its histological features nor in its degree is syphilitic endarteritis a distinctive lesion. Tuberculous endarteritis is not uncommon in the lung in association with fibroid phthisis and in other tuberculous lesions such as tuberculous lymphatic glands.

A similar lesion is found in other inflammatory lesions, as, for instance, in the vessels at the base of a perforating ulcer occurring in syringomyelia; and Dr. Spilsbury has given me a very good specimen of a peptic ulcer in the base of which is an artery which shows well-marked intimal thickening together with *marked hyperplasia of the internal elastic lamina.*

There is a second type of chronic endarteritis in which there occurs a proliferation and splitting of the internal elastic lamina into several distinct layers. I have one specimen of this prepared from a frontal lobe, the site of gummatous infiltration. In this artery there is marked subendothelial proliferation leading to a high degree of narrowing of the lumen and at the same time a splitting of the internal elastic lamina into two layers. My best specimen, given by Dr. Spilsbury, is taken from a rabbit's lung which was studded with miliary tubercles (human), injected four months before death for diagnostic purposes. The animal was killed because it was eating too much and growing too fat, facts which indicate the chronicity and low virulence of the infective process. The sections, one of which is drawn in Fig. 6, Plate 6, shows a hyperplastic sclerosis of the branches of the pulmonary artery, and the prominent feature is a marked hyperplasia and splitting of the internal elastic lamina identical with the histological picture of diffuse hyperplastic sclerosis.

(d) *Degeneration.* There is no need to bring forward evidence that hyaline and fatty degeneration result from singly acting causes of disease. The presence of degeneration in itself indicates a failure on the part of the affected tissue to react to or resist a *materies morbi.* Only one point need be made, namely, the distinction between atrophy and degeneration. Atrophy may be physiological, as when it is a part of the process of involution; degeneration is pathological. A typical example of fatty degeneration without proliferative changes was found in sections of a tuberculous spleen where there was fatty obliteration of arterioles associated with the tuberculous lesions in the organ. The normal sequence in arterial degeneration is hyaline degeneration followed by fatty degeneration. Hyaline degeneration does not always progress to fatty degeneration, and an advanced stage of the latter may occur without evidence of the former. There is a good illustration of advanced hyaline degeneration in the arterioles of a lymphatic gland in Thoma's *Text Book of Pathology*, p. 385. I found a similar condition of advanced hyaline degeneration in an artery in Dr. Thursfield's collection of microscopical specimens. It is the section of an artery in the middle of a lymphadenoma gland that had undergone hyaline degeneration. The specimen shows complete obliteration of the lumen of a second size artery; the lumen is occluded by a hyaline mass which I interpret as hyaline degeneration of a vascularized thrombus; endothelial cells, red blood corpuscles, and four arterioles, all of which have undergone hyaline degeneration, are also seen. In addition there are a few cells, mononuclear and endothelial cells, which are yet intact.

Such specimens are uncommon, and fatty degeneration is characteristic of arterial degenerative change, and it is by the presence of fat in an arterial wall that the activity of a pathological process is established.

(iii) *New growths.* The arterial changes in tumours are of importance and require separate description, since it is not obvious in all cases whether the changes observed are of the nature of growth, involution, or inflammation. My interest in tumours arose in the search for examples of arterial involution. Vascular lesions in tumours are well recognized, and I have come to the conclusion that the underlying process in their production is inflammatory. Thus, in my series of sections all four types of endarteritis (used in a limited sense) are represented, and any arterial lesions in tumours that I have seen are explainable in terms of these four types. The example of acute endarteritis occurring in a fibrolipoma has already been described. The more common type of acute endarteritis, in which the whole arterial wall is penetrated by cellular infiltration, and in which there is no intimal hyperplasia or fatty degeneration, is often found in tumours. For an example of chronic endarteritis of the syphilitic type I am indebted to Dr. Spilsbury. The sections were prepared from a lymphatic gland invaded by metastases from an epithelioma of the tongue; the smaller arteries show a marked intimal hyperplasia without thickening or proliferation of the internal elastic lamina. The second form of chronic endarteritis, in which there occurs a thickening and splitting of the internal elastic lamina in addition to the sub-endothelial hyperplasia, is illustrated in sections made from an epithelioma of the tongue and in others made from a fibrosarcoma of the sciatic nerve. This type of chronic endarteritis is typical of the changes seen in the second size arteries of diffuse hyperplastic sclerosis.

(iv) *Histological evidence on the aetiology of arterio-sclerosis.* In local hyperplastic sclerosis of the active inflammatory type, whether acute or chronic, there may be no small-cell infiltration of the arterial walls; in fact, as in diffuse hyperplastic sclerosis, small-cell infiltration is characteristically absent. A distinction has been made between the microscopical appearance of hyperplastic sclerosis of known inflammatory origin and that of diffuse hyperplastic sclerosis. Jores especially emphasizes this distinction, though recognizing intermediate forms; Sir Frederick Andrewes has written in the same sense (*loc. cit.*, p. 232), and points out that the two types tend to run into one another and even to occur in combination. My specimens, especially that of miliary tubercle in the rabbit's lung, confirm the histological identity of local endarteritis and diffuse hyperplastic sclerosis. Whether or not the internal elastic lamina undergoes hyperplasia and splitting in an inflammatory reaction may depend largely on the chronicity of the process. A comparison, therefore, of the microscopical changes seen in local hyperplastic sclerosis of known inflammatory origin with those seen in diffuse hyperplastic sclerosis provides histological evidence in favour of the view that the underlying process in the production of arterio-sclerosis is one of active inflammation.

A second piece of evidence for the inflammatory nature of arterio-sclerosis results from a consideration of the nature of the intimal thickening in hyperplastic sclerosis. The type of acute endarteritis described on p. 233 is characterized by endothelial proliferation. The specimen, in which the changes characteristic of

acute and chronic endarteritis are simultaneously present in the same artery, shows that a part of the intimal thickening in chronic endarteritis is of endothelial, as distinct from subendothelial origin. It is conceded by many pathologists that a metaplasia of endothelium into fibrous tissue may occur, and the opinion that a part of the intimal thickening in arterio-sclerosis results from endothelial proliferation is held by Klotz and Andrewes. The intimal thickening in arterio-sclerosis has sometimes the appearance of being formed, in part at any rate, of proliferated epithelial cells. A section of a second size splenic artery is drawn in Fig. 7, Plate 4. The intima has undergone complete fatty degeneration, but the vague outline of flattened endothelial cells is still visible. If the proliferated endothelial cells seen in the artery of Fig. 3, Plate 4, were flattened against the arterial wall and were then to undergo fatty degeneration, one imagines that the intima in Fig. 3 would resemble the intima in Fig. 7. The proliferation of endothelial cells in acute and chronic endarteritis and diffuse hyperplastic sclerosis brings these three forms of arterial disease into line and is additional evidence in favour of their explanation in terms of one unit process, inflammation.

The presence of fatty degeneration in arterio-sclerosis is no difficulty to the inflammatory theory of causation. A *materies morbi* of greater virulence acting on tissue of lesser resistance will cause a degenerative change in that tissue; if the tissue has a greater degree of resistance it will resist the action of the *materies morbi*, and in fact be stimulated by its presence to inflammatory reaction. The resistance of a tissue to a pathogenic agent depends very largely on the efficiency of its blood-supply. I visualize the incidence and nature of diffuse hyperplastic sclerosis affecting the intimate vasculature of an organ as a fairly uniform fatty obliterative endarteritis affecting terminal arterioles; this fatty degeneration spreads backwards to cease abruptly at the origin of the arteriole from its parent artery in whose walls no fatty degeneration occurs, but, instead, a marked inflammatory reaction shown in intimal hyperplasia. It is possible that (remembering that arterial walls are relatively avascular tissues) owing to a change in arteriole endothelium the arteriole under certain conditions loses its supply of oxygen and fatty degeneration results; under the same conditions its parent artery, never having relied for its oxygen supply on the blood in its lumen, finds sufficient oxygen for its needs in its perivascular lymphatics or capillaries. This hypothesis explains, in the meantime, why the same pathogenic agent leads to fatty degeneration in an arteriole and inflammatory reaction in its parent artery.

Although the unit process inflammation is thus sufficient explanation for the histological changes seen in arterio-sclerosis it is obvious that the physiological processes, growth and involution, may play their part. The absence of fatty degeneration, however, in growth and involution rules out these processes as determining arterio-sclerosis. With regard to the unit process, growth, the following *a priori* argument is of academic importance. It is accepted in current medical teaching that healthy heart-muscle is not damaged by any form of healthy activity—in other words, heart disease does not result from physical strain. For the same reasons as this opinion is accepted it is to be expected that,

since the normal function of arterial walls is to withstand a definite internal pressure, an increase of this pressure by 200 per cent. will be equally incapable of causing pathological changes in the structure of the arterial wall.

To explain the relative incidence of diffuse hyperplastic sclerosis in the several organs of the body other considerations may be of importance. The pathology of infarction has led to the opinion that the brain, kidneys, spleen, and heart are supplied by 'end arteries', whereas in the case of other organs a more complete arterial anastomosis occurs. As regards the kidney, spleen, and brain there is no doubt of the truth, on anatomical grounds, of this opinion, but it is not, at the same time, certain that the intimate vasculature of the organs mentioned differs in anything more than degree from that of other organs presumed not to be supplied by 'end-arteries'. Hunter's dictum has not been controverted; he wrote as follows: 'We may observe, perhaps as a general principle, that arteries near their destination do not anastomose.' The difference, then, between the terminal arterioles, say of the liver and those of the brain, may be simply a question of their length; all terminal arterioles are necessarily 'end-arteries'. Nor is the question of the length of an arteriole the only consideration of importance, for, as J. L. Shellshear has pointed out, the angle at which terminal arterioles are given off from their parent trunk, and the capillary pressure in the area they supply, are important factors in determining rate of blood-flow through them. These factors must play a part in determining the incidence of arterio-sclerosis. The absence of a fatty obliterative endarteritis in the heart is of interest. Whether the arterial anastomosis in this organ is good or not is a matter on which I have no observations, but it is evident, from the poverty of small arteries in any section of heart-muscle, that terminal arterioles are short. It may be a factor of more importance than the length of the terminal arterioles in the heart that the pulse in this organ occurs in diastole, so that both in the filling and emptying of its vessels the flow of blood is reinforced by the cardiac dilation and contraction. For comparison one may imagine an artificial circulation through a sponge and its reinforcement by squeezing out the sponge between each stroke of the pump as in some measure illustrating the difference between the circulation through the general organs of the body on the one hand and through the heart on the other hand. In the second place, the capillary net-work in the heart-muscle is very finely meshed; if more finely meshed than any other organ this would be an additional factor in maintaining an absolutely efficient and rapid circulation in spite of slight arterial or capillary disease. These are the considerations which have led me to the conclusion that the distribution of the fatty degeneration in the several organs and in the particular parts of the intimate vasculature of these organs depends on the maintenance of an efficient circulation through vessels at a time when perhaps they are, and in spite of the fact that they are, invisibly damaged by disease. It is not imagined that the toxin which causes arterio-sclerosis has a selective action on arterial tissue; the absence, except in the case of glomerular tufts, of capillary change in most cases of diffuse arterial disease is probably due to the fact that

nature places diseased tissues at rest; hence capillaries contract out of sight at the earliest insult of the *materies morbi*. Fatty degeneration of capillary walls is sometimes seen. Finally, the distribution of diffuse hyperplastic sclerosis may have a physiological significance. The frequency and intensity of the lesion in the kidney and spleen may depend on the function of these organs rather than on the anatomical factors involved in their vasculature. There is evidence that both the kidney and spleen are active in removing bacteria from the blood-stream, and in performing this function their intimate vasculature may suffer damage.

D. *The Relation of Diffuse Hyperplastic Sclerosis to Senile Arterio-sclerosis.*

Senile arterio-sclerosis is characterized histologically by the presence of fatty degeneration in the media. The senile form of arterio-sclerosis may be associated with diffuse hyperplastic sclerosis, but in itself does not tend to diffuse intimal thickening of anything more than slight degree, except in its incidence on the larger arteries, in which it may have all the histological features of nodular sclerosis.

It is noted in this connexion that Cazalis's aphorism, 'On a l'âge de ses artères', has led some authors to regard senile arterio-sclerosis as an expression of the general involution of old age. Histologically, *senile arterio-sclerosis has nothing in common with involution*; fatty degeneration is the main feature of the former, intimal hyperplasia is the prominent feature of the latter; the one is primarily medial, the other intimal. *Senile arterio-sclerosis is one of the few forms of arterial change from which involution can be excluded as an active process in its production.*

As regards the intimate vasculature of organs, except in certain definitely toxic conditions, fatty degeneration of the media rarely occurs under the age of 50. The tabulated results of the condition of the intimate vasculature of hearts bear on this point. In no less than nine of the fifteen cases over 50 years old there was fatty degeneration of the media. This lesion was not found in any hearts less than 50 years old.

In general, fatty medial degeneration is not associated with marked intimal hyperplasia, or where such intimal hyperplasia occurs it is local and limited to one part of the circumference of the vessel. In some cases it is, however, associated with diffuse hyperplastic sclerosis, as when the latter lesion occurs in an elderly patient.

It has been pointed out by Aschoff, Gaskell, and others that the distribution of the lesion in the vascular tree is distinctive, that senile arterio-sclerosis tends to fall on the larger arteries and diffuse hyperplastic sclerosis on the smaller arteries or intimate vasculature. As regards naked-eye examination I agree with this distinction. If, however, fine degrees of fatty medial degeneration in the smaller and smallest arteries are the first evidence of senile arterio-sclerosis, then certainly senile arterio-sclerosis is diffuse in its distribution. It is even more diffuse in its distribution than diffuse hyperplastic sclerosis, because the main trunks are greatly

affected and the intimate vasculature microscopically affected. The distinction may still be maintained that diffuse hyperplastic sclerosis does not affect the larger trunks to a considerable degree. They are undoubtedly affected to some extent in an intimal thickening in which fatty degeneration is prone to occur; further, a considerable, even advanced, degree of arterio-sclerosis of the main vascular trunks (especially the arteries at the base of the brain, but also the carotids and aorta) is not uncommon in typical diffuse hyperplastic sclerosis.

The age incidence of the two conditions is different, as has already been noted; senile arterio-sclerosis is rare before 50 and increases in frequency with increasing years; diffuse hyperplastic sclerosis is uncommon before 35 and rare after 75 years. Sir Clifford Allbutt has established the clinical types of these two arterial lesions, the senile type associated with a normal or only little raised blood-pressure and corresponding heart-weight, the diffuse hyperplastic sclerosis type with definitely raised blood-pressure and great cardiac hypertrophy.

In the clinical aspects and histological features there is a clear distinction between these two types of arterio-sclerosis. The age difference, the fatty medial degeneration in one, and the intimal hyperplasia without fatty medial degeneration and association of raised blood-pressure and cardiac hypertrophy in the other are clear distinctions. These distinctions are not sufficient to justify the assumption of different causative factors in the two conditions. The frequent association of diffuse hyperplastic sclerosis and senile arterio-sclerosis in the same patient, in the same histological picture, and the overlap in age are equally explicable in terms of identical pathogenic factors resisted by and reacted to by tissues of different age. *It is a question of varying physiological age response rather than a difference in the pathogenic factors involved.* In these terms one is led to regard the vitality of the endothelium as the critical factor. Its power of proliferation may be the factor that protects the media from toxins circulating in the blood; impaired vitality of the endothelium, particularly as the result of age, may render the media open to damage by circulating toxins. The possibility of a different blood-supply to endothelium as distinct from the rest of the arterial wall, including the subintimal layer, is of interest from this point of view.

The foregoing remarks are speculative, but the subject is discussed in order that diffuse hyperplastic sclerosis may not appear as a pathological entity in arterio-sclerosis. Its separate treatment in this communication tends to isolate it from other forms of arterio-sclerosis, and, though such isolation is convenient in study, there is no reason for regarding the distinction as hard and fast in fact.

2. Clinical Aspects of Diffuse Hyperplastic Sclerosis.

A. *Cardiac Hypertrophy.*

There are three causes of cardiac hypertrophy, namely, organic heart disease, chronic pulmonary disease, and increased resistance in the systemic circulation. The first two conditions are established principles, the last-named condition is to a certain extent an assumption. All cases are excluded in which organic heart disease or chronic pulmonary disease were known to be present except it is stated to the contrary. This holds good equally for the statistical material. Chronic pulmonary disease and disease of the pericardium and endocardium are easy of recognition and exclusion; chronic myocardial disease is less readily recognized, and it is therefore likely that it is a factor in the production of cardiac hypertrophy in many cases. Cases of emphysema are included.

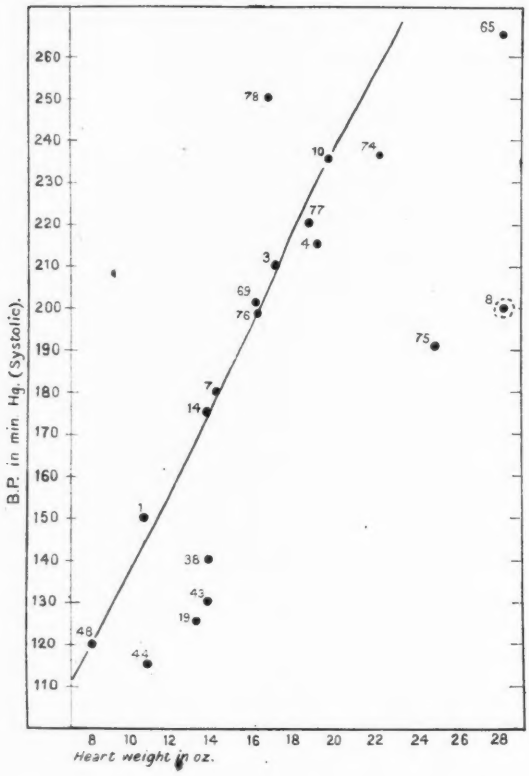
(i) *Critical standard of cardiac hypertrophy.* In order to avoid the inclusion of cases of cardiac hypertrophy due to slight unrecognized lesions of the heart and lungs, and on account of the difficulty of determining the actual degree of ventricular hypertrophy, whether by measurement of the thickness of the ventricular wall or by weighing the isolated ventricle, lesser degrees of cardiac hypertrophy have been excluded.

In going through the medical post-mortem records of St. Bartholomew's Hospital for the last twenty years I found that a 15 oz. heart-weight forced itself on my notice as a significant figure. Whereas heart-weights of all degrees up to 15 oz. were of common occurrence, in cases whose hearts weighed more than 15 oz. the post-mortem findings and associated conditions tended to group themselves into definite groups of pathological entities. It seemed that cardiac hypertrophy up to 15 oz. might result from unobtrusive conditions such as a body-weight above the average, excessive fatty infiltration, perhaps unusual physical activity during life or even pathological states in early phases that escape recognition. Cardiac hypertrophy above 15 oz. was, on the other hand, commonly associated with a familiar pathological state.

More recently in compiling a graph to show the relation of heart-weight to blood-pressure the significance of the 15 oz. standard was confirmed (in so far as so few cases afford confirmation); the tabulated results showing the relation of diffuse hyperplastic sclerosis to cardiac hypertrophy also emphasize the importance of the arbitrary standard taken.

(ii) *Cardiac hypertrophy in relation to raised blood-pressure.* In eighteen cases a record of blood-pressure had been taken on one or more occasions. The systolic pressure only is noted in each case, because, though perhaps of less importance than the diastolic, its values at present convey more information and its measurement is less liable to error. The heart-weights and systolic pressures are plotted on the following graph:

Chart I.



A straight line was drawn joining Case No. 48 to Case No. 10, these being the highest and lowest heart-weights of the series at the time at which this chart was first compiled; successive cases were added as they occurred. The cases group themselves about this line, indicating a casual sequence, rather than mere association, between cardiac hypertrophy and raised blood-pressure. There is an exception to this regular grouping about the straight line in the group of four cases whose hearts weighed 10½ to 13½ oz. This group of cases confirms the importance of not attaching significance (from the point of view of the present study) to heart-weights under 15 oz.; it allows a margin of 1½ oz. for faulty weighing, variations in the length of aorta left attached to the weighed heart, &c. Case No. 8 suffered from marked aortic regurgitation and is inserted in order to illustrate graphically the dislocation to the right that results from coincident heart disease. Cases Nos. 75, 65, and 78 also vary widely from the mean of the majority of cases. The positions of Cases Nos. 75 and 78 are no doubt affected by the fact that the former was a very big man and the latter very small.

(iii) *Cardiac hypertrophy in relation to diffuse hyperplastic sclerosis.* Post-mortem records are not available as evidence on this subject, because they

deal only with arterial change in the larger trunks, or when reference is made to changes in the intimate vasculature of organs it is too limited to be of value. As regards the larger trunks, such as the aorta, iliac arteries, coronary arteries, and vessels of the circle of Willis (the arteries whose condition is most commonly reported), there is no close relation between the degree of cardiac hypertrophy and the degree of arterio-sclerosis. A good example of this fact is the absence of cardiac hypertrophy in aneurysm of the aorta. Allbutt has shown that one form of arterio-sclerosis, his 'decrescent or involutionary' arterio-sclerosis, is not accompanied by cardiac hypertrophy. In fact the absence of cardiac hypertrophy is one of the distinctive features of this form of arterio-sclerosis and its chief incidence is on the larger vessels.

In the present research there is certain material available for judging the relation of cardiac hypertrophy to diffuse hyperplastic sclerosis. The amount of diffuse hyperplastic sclerosis was determined on the basis of its degree and its distribution in the several organs of the body. In the table that follows the sign + indicates a marked incidence of the lesion in one organ or definite incidence in more than one organ; the sign + + indicates a marked incidence of the lesion in more than one organ. The distribution of the lesion was set out from the original records of histological observation in a table that included every organ examined in every case in the series.

The cases taken are those in which the intimate vasculature in a series of organs was examined *post mortem*. The results are summarized in the following table:

Cases in which there was definite diffuse hyperplastic sclerosis.

No. of Cases.	Average Heart-weight.	Degree of Arterial Lesion.
14	19·9 oz.	+ +
8	13·9 oz.	+

Cases with cardiac hypertrophy without diffuse hyperplastic sclerosis.

1	14·7 oz.	0

Cases without cardiac hypertrophy with diffuse hyperplastic sclerosis.

8	12·3 oz.	3 = + + 5 = +

There was no case of a heart weighing 15 oz. or more in which there was not some degree of diffuse hyperplastic sclerosis. In this series of fourteen cases of hearts weighing more than 15 oz. diffuse hyperplastic sclerosis was present in every case.

It is not presumed that this vascular lesion is necessarily present in every case of cardiac hypertrophy (without heart or pulmonary disease) beyond 15 oz. The case whose heart weighed $14\frac{3}{4}$ oz. without there being found any sign of diffuse hyperplastic sclerosis was an alcoholic, and though it is excluded by $\frac{1}{4}$ oz. from the cases with cardiac hypertrophy, the 15 oz. standard of cardiac hypertrophy is arbitrary, and $\frac{1}{4}$ oz. is of little account considering the rough way in which the hearts were weighed. Hence, though certain factors such as alcoholism may prevent the rule being absolute, there is evidence that cardiac hypertrophy above 15 oz. indicates the presence of diffuse hyperplastic sclerosis (cases of chronic heart and pulmonary disease being excluded).

The reverse proposition does not hold good, that is to say, diffuse hyperplastic sclerosis may be present without marked cardiac hypertrophy. Of the eight cases in which the arterial lesion was present and the heart weighed less than 15 oz. no less than 5 died of uraemia. In two cases the arterial lesion was present in the kidney, spleen, brain, and liver, and absent in the heart, skeletal muscle, stomach, small and large intestine, and suprarenal gland. The hearts weighed 13½ and 14½ oz. respectively and both cases died of cerebral haemorrhage. In these two cases there was sclerosis of the arteries of the medulla, and they are evidence that diffuse hyperplastic sclerosis affecting the arteries in this region is not the determining factor in cardiac hypertrophy. The eighth case of this group showed a widespread arterial lesion, though very slight in degree. Death was due to cerebral haemorrhage.

(iv) *Interpretation of these observations.* The fact that cardiac hypertrophy above 15 oz. is always associated with diffuse hyperplastic sclerosis, and the fact that diffuse hyperplastic sclerosis may occur without cardiac hypertrophy, are evidence to some extent of cardiac hypertrophy, that is to say of raised blood-pressure, being a cause of the vascular lesion. This interpretation requires adequate notice, but at the same time is at variance with other observations in this research. An alternative interpretation is possible in terms of a pathogenic agent which in its effect on capillary walls increases the resistance to the flow of blood with resultant cardiac hypertrophy, and this pathogenic factor may or may not simultaneously affect arterioles and smaller arteries.

These observations lead to the conclusion that cardiac hypertrophy found *post mortem* is good evidence of a raised blood-pressure during life, and the weight of the heart gives an indication of the previous height of the blood-pressure. Since the relation of cardiac hypertrophy to diffuse hyperplastic sclerosis has been established a second conclusion follows—that is, *a persistent systolic pressure of 190 mm. Hg or over is evidence of diffuse hyperplastic sclerosis.* This statement raises the question of the significance of the term hyperpiesia. Hyperpiesia is a clinical condition in which a patient suffers from a persistently raised blood-pressure though showing no sign of renal disease. Renal sclerosis may, as is well known, be found *post mortem* though the urine during life was normal, and two such cases occurred in my series. The pathology of hyperpiesia does not therefore centre round renal sclerosis. In the meantime I regard hyperpiesia as the clinical expression of diffuse hyperplastic sclerosis. Hyperpiesia is, in fact, a form of arterio-sclerosis, and a persistently raised systolic pressure of 190 mm. Hg or over is the only adequate clinical sign of diffuse arterial disease. Hyperpiesia would be proved a clinical entity distinct from arterio-sclerosis if in a body whose heart weighed more than 15 oz. (and not subject to chronic heart or lung disease) a systematic examination of the intimate vasculature of the several organs proved the absence of diffuse hyperplastic sclerosis.

Finally, the conclusions now arrived at allow of the examination of certain possible aetiological factors in diffuse hyperplastic sclerosis on the basis of the presence of cardiac hypertrophy.

(v) *Cardiac hypertrophy in relation to chronic renal disease.* The problem may be stated in the form of a question, thus: *Does chronic renal disease 'cause' cardiac hypertrophy?* The accepted answer is undoubtedly 'yes', and the clearest evidence is the not uncommon occurrence of cases of cardiac hypertrophy without heart or lung disease, but with chronic kidney disease occurring at an age when arterio-sclerosis is extremely rare. In this, clinical experience is supported by pathological examination *post mortem.*

Evidence from single cases. Case No. 39. Female, aged 31, died of intercurrent septicaemia. History of renal oedema and diagnosed during life as a chronic parenchymatous nephritis of the sclerotic type—that is, a 'contracting white kidney'. *Post mortem*: Heart-weight 12 oz. Kidneys, Rt./Lt., 3/2 oz. 'Small white kidneys', granular; typical. Confirmed by microscopic examination.

Case No. 43. Female, aged 46, died of uraemia of the chronic gastro-intestinal type. Six years' history of bilious attacks and no history of oedema. *Post mortem*: Heart-weight 13½ oz. Kidneys, Rt./Lt., 2¼/1¼ oz. Hard, pale, shrunken, typical 'small white kidneys'; almost complete absence of cortex. Histological examination showed very advanced chronic interstitial nephritis; in my opinion a 'contracted white kidney', using the term in contradistinction to a 'contracting white kidney'.

Case No. 1. Male, aged 29, died of uraemia of the latent type. Dr. Herringham compared the clinical condition to diabetic coma. *Post mortem*: Heart-weight 10½ oz. Kidneys: Rt./Lt., 0/3¼ oz. No right kidney. Left very small, globular in shape, and tough on section; little cortex, surface very granular. Histology showed an advanced degree of chronic diffuse nephritis.

Case No. 44. Female, aged 53, diagnosed polycystic kidneys two years before death, died of uraemia. *Post mortem*: Heart-weight 10½ oz. Both kidneys much enlarged, a mass of cysts. Histological examination revealed little renal tissue and what secreting tissue was left showed marked chronic interstitial inflammation.

These four cases of extreme chronic renal disease without marked cardiac hypertrophy (the hearts weighed 12, 13½, 10½, and 10½ oz.) are evidence that renal disease *per se* does not produce cardiac hypertrophy. In the remaining cases of chronic renal disease of marked degree in my series there was an associated cardiac hypertrophy.

Statistical evidence bears out the general opinion that chronic renal disease causes cardiac hypertrophy and shows the four cases already described to be exceptions.

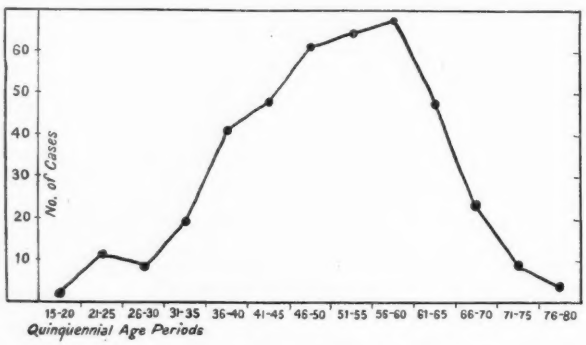
Evidence has been taken from two points of view. In the first place, a graph of heavy hearts was made and the changed form of the graph that results from withdrawing certain cases of chronic renal disease noted. In the second place, a list of certain chronic renal diseases was compiled and the respective heart-weights tabulated. This second chain of evidence was compiled by A. H. Little for his M.B. thesis (1920).

The data which forms the basis of statistical evidence brought forward in this research were collected from the twenty years' St. Bartholomew's Hospital medical post-mortem records of the years 1895–1914 inclusive.

The first group of cases to be considered includes all cases in which the heart weighed more than 15 oz., exclusive of cases in which there was evidence of organic heart disease or chronic pulmonary disease; few cases required exclusion on the latter count. The group comprises 404 cases tabulated in the form of a graph in Chart II. The cases are summed into quinquennial age periods and plotted in a graph of which the ordinates represent the number of hearts dying in the several age periods which are plotted on the base-line.

If cardiac hypertrophy were the result of the action of a single cause, or if this group of hypertrophied hearts belonged to a single clinical series, it would be expected that the curve would show uniformity. It is seen, however, that the curve rises to a maximum at the quinquennium 56–60 years, with a distinct bump at 21–25 years and again at 36–40 years. The downward curve is uniform.

Total No. of Cases of Cardiac Hypertrophy dying in Quinquennial Age Periods. 1895–1914. Chart II.



(It is noted that in the records of these 20 years are several cases of pernicious anaemia with cardiac hypertrophy without other post-mortem evidence of the presence of conditions generally associated with cardiac hypertrophy. Cabot has recently reported on the association of cardiac hypertrophy with pernicious anaemia.)

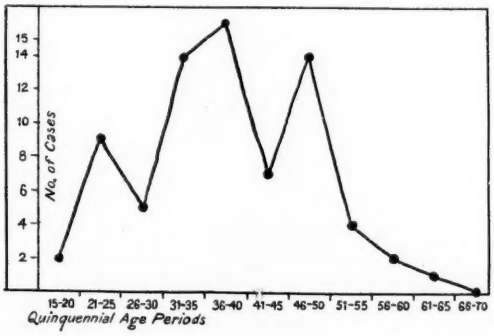
These irregularities suggest the inclusion of subsidiary groups in a main group.

Now it is commonly accepted that chronic renal disease causes cardiac hypertrophy; the only difficulty is to determine from post-mortem description, or label, with what form of kidney disease particular cases suffered. I have made the broad distinction recognized by clinicians and pathologists between kidney disease occurring in the first half of life and kidney disease occurring after forty years, and have based this distinction on the label given to particular kidneys by the morbid anatomist who conducted the post-mortem examination. Though the different terms applied to kidney lesions have various meanings, the terms are generally used in a definite sense in a single medical school even over a period of twenty years. All kidneys are classified in the first group (with the earlier age incidence), to which any of the following descriptive terms are

applied: large white, small white, contracting white, contracted white, secondary contracted white kidney; parenchymatous, chronic parenchymatous, chronic diffuse, mixed, chronic mixed, chronic nephritis; polycystic kidney. It appeared from a survey of these twenty years' records that the above terms expressed a form of renal lesion commonly occurring at a relatively early age and commonly regarded as primarily renal disease, a form distinct from a group of kidney lesions described in any of the following terms occurring at a later age, and regarded by many as primarily vascular in origin: small red, granular, gouty, senile, arterio-sclerotic kidney; chronic interstitial nephritis.

All cases of cardiac hypertrophy in which there was a kidney lesion belonging to the first group of kidney cases were tabulated, and the summary of these cases forms Chart III. The graph has the same abscissae and ordinates as Chart II. It comprises seventy-four cases. If these were all of one type its form might justify comment, but since various forms of chronic renal lesion are without doubt included in the single series the number of cases is too few to form the basis of observation. It is noted that no cases of simple cloudy swelling or toxic nephritis (Gaskell's tubular form) are knowingly included in this series, nor as a matter of fact are there any cases in it of acute nephritis (Aschoff's acute glomerulo-tubular nephritis).

Number of Secondary Contracted Kidneys with Hypertrophied Hearts dying in Quinquennial Age Periods. 1895–1914. Chart III.



The next step is to subtract the cases in Chart III from the main group in Chart II. The residue of cases is shown in Chart IV. Chart IV, therefore, comprises all cases of cardiac hypertrophy above 15 oz., excluding cases of supposed primary renal disease.

For convenience of comparison Chart II is superimposed in dotted lines on Chart IV. It is now seen that the first bump in Chart II is flattened out and the initial part of the graph up to the quinquennium 31–35 *is a straight line but not a horizontal or zero line.*

In the terms of the interrogation put at the beginning of this subsection Chart IV supplies a direct answer: up to the age of 35 chronic renal disease is

the commonest cause of cardiac hypertrophy. It is evidently not the only cause. Some other factor is at work, and, in so far as these observations go, it is probably a unit factor, because the graph is a straight line up to the age of 35 years. The number of cases is, however, too few to justify further comment.

Cases of Cardiac Hypertrophy from which Primary Kidneys are excluded. 1895–1914. Chart IV.

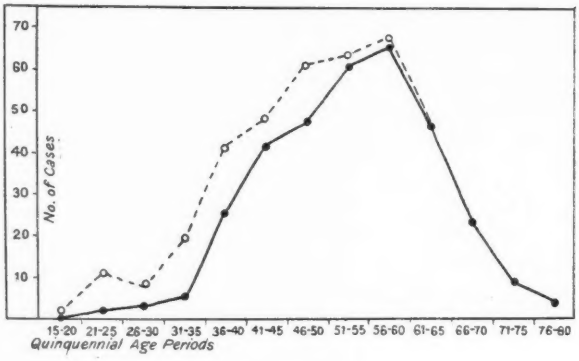
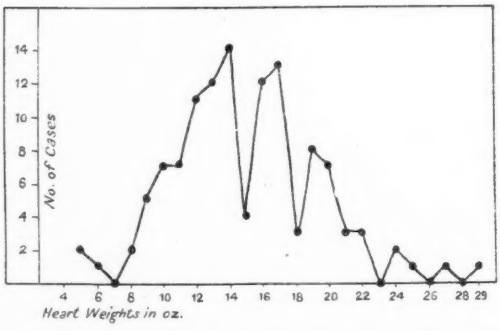


Chart V.



So far, then, there is direct evidence that chronic primary kidney disease is a cause of cardiac hypertrophy—that is, of diffuse hyperplastic sclerosis. This record of cases supplies the clearest mass evidence that I know of in support of accepted clinical and pathological teaching on the relation of chronic nephritis to cardiac hypertrophy and arterio-sclerosis.

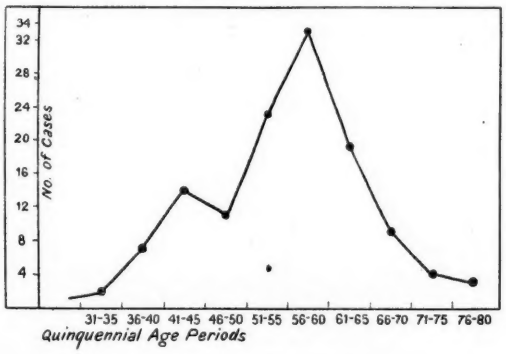
A. H. Little, taking the same years' sequence of St. Bartholomew's Hospital post-mortem records, approached the subject from a different angle. He took all the cases of primary chronic renal disease of whatever heart-weight and tabulated them. One of his charts bears directly on the present subject. The chart in question shows in the form of a graph the number of cases of chronic primary kidney disease dying with hearts of various weights. The chart is shown here numbered Chart V. Cases under 20 years of age and cases described as having large white kidneys are excluded.

Many errors unavoidably occur in the tabulation of such cases. Large white kidneys are often described by the pathologist as chronic parenchymatous nephritis; many cases of chronic interstitial nephritis are doubtless included in the term chronic diffuse nephritis. The evidence, therefore, is only acceptable as corroboratory evidence.

The following conclusions seem justified: Many cases of chronic kidney disease are unaccompanied by marked cardiac hypertrophy. Some degree of cardiac hypertrophy occurs in the great majority. The proportion of cases in which the heart weighed up to and including 15 oz. to those in which the heart weighed more than 15 oz. is as sixty-five to fifty-four.

Chronic renal disease, therefore, excluding cases under 20 years of age and kidneys labelled as 'large white', produces cardiac hypertrophy in 45 per cent. of the cases in this series. This statement is not final and will be re-examined in a subsequent section.

Total Cases of Cerebral Haemorrhage with Cardiac Hypertrophy. 1895–1914. Chart VI.

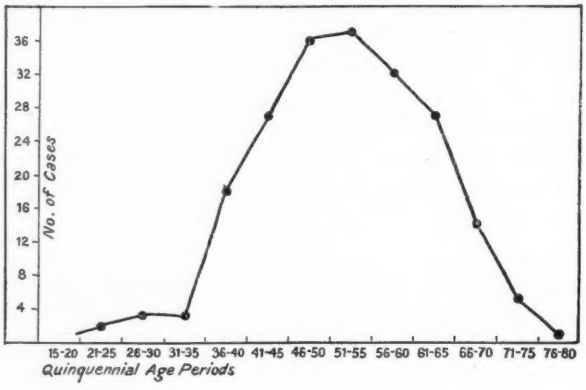


(vi) *Cardiac hypertrophy in relation to syphilis.* Chart IV is brought forward for further consideration. The upward curve has a single bump at the quinquennial age period 41–45 years. This irregularity is slightly more evident in the graph which comprises the cases dying of cerebral haemorrhage; these are plotted in Chart VI, which includes 125 cases. Now, if the increased case mortality at 41–45 years is due to the inclusion of a pathological group that dies of cerebral haemorrhage, the subtraction of all cases dying from cerebral haemorrhage from the main group should flatten out the upward curve in the latter chart. This is in fact what happens, and Chart VII gives the remaining cases of cardiac hypertrophy after subtracting chronic primary kidney disease *and* cerebral haemorrhage. The upward curve is a straight line, and the graph becomes nearly symmetrical. Syphilis is a known aetiological factor in the causation of cerebral haemorrhage at an earlier age than the maximum age incidence of cerebral haemorrhage from other causes.

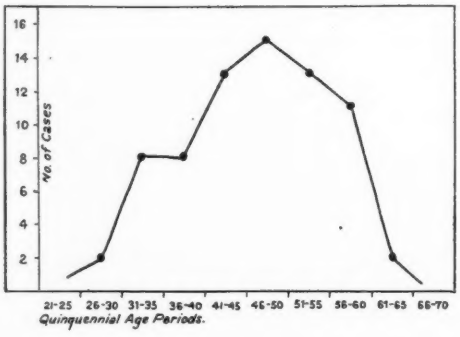
Further, syphilis is a proved cause of vascular disease and, in particular, is the

commonest actual cause of aneurysm of the aorta. It is, therefore, fair in statistical records to assume that syphilis is the cause of aortic aneurysm. During the same twenty years seventy-three cases died with aneurysm of the aorta. These cases are plotted in the form of a graph in Chart VIII.

Chart VII.



Seventy-three Consecutive Cases of Aneurysm of the Aorta. Chart VIII.

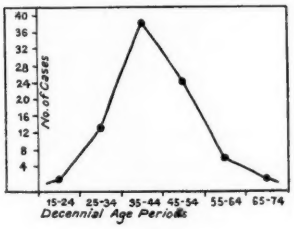


The maximum age incidence of death from aneurysm in these cases falls in the quinquennium 46–50. Of these seventy-three cases no less than seven died at the age of 46; five died at the age of 41; four died at the ages of 38, 49, 53, 56, and 60; three died at the ages of 35, 43, 44, 51, 54, and 57. The cases are too few to permit of emphasis being laid on death at a single age, and it is justifiable to regard the great case mortality at 46 years as fortuitous. If two of these cases had died one year earlier the peak of the graph would have been in the quinquennium 41–45 years; in this event the maximum case mortality of death from aneurysm of the aorta would have fallen in the same quinquennium as the bump on the upward curve of the case mortality chart of cardiac hypertrophy.

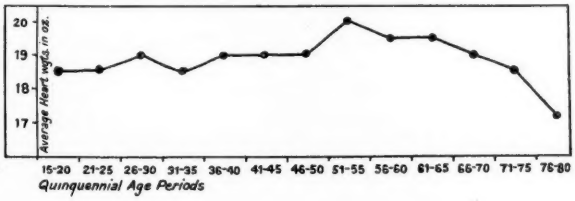
This line of reasoning is supported by Browne's figures of the case mortality of eighty-eight cases of aneurysm of the aorta. The figures are not exactly comparable to mine as his figures are massed in decennial periods and are one year different to my periods. I have put his figures together in the form of a graph (*vide* Chart IX) which shows the maximal case mortality in the (decennial) 35–44 age period.

Aneurysms of the Aorta—from Oswald Browne.

Case Mortality. Chart IX.



Average Heart-weights of all Cases of Hypertrophied Hearts in Quinquennial Age Periods. 1895–1914. Chart X.



This evidence points to syphilis as a cause of the increased mortality of hypertrophied hearts about the age of 45. The same evidence points to syphilis as a cause of cardiac hypertrophy and diffuse hyperplastic sclerosis, with a maximum effect at this age period.

It is generally taught that vascular tissue loses its power of response to increased pressure with advancing years. The heart-weights of the individual cases dying in the several quinquennial periods have been summed and averaged. The result is shown in the graph on Chart X; the curve is a relatively straight line varying little from 19 oz. average. Cardiac hypertrophy is able to attain the same average degree at any age period up to 75 years.

B. *Cerebral Haemorrhage in Relation to Diffuse Hyperplastic Sclerosis.*

Ten cases in my series died of cerebral haemorrhage. Although the number is small the cases form a very representative group. One is excluded from further consideration, being a case of malignant endocarditis affecting the aortic valves in a man aged 27. The remaining cases are tabulated so that the points of chief importance in each case are readily compared.

As is usual in hospital statistics, males preponderate excessively in my series, namely, as 7 : 2. Andrewes has called attention to the fact that the incidence of cerebral haemorrhage is in reality equal in the sexes. The age incidence varies between 36 and 76. Of aetiological factors it is noted that one case was a painter, two were alcoholic. In the remaining cases the history, when available, was of no special import. The Wassermann reaction was only done in two cases, of which one was positive. The haemorrhage was capsular in six, subarachnoid in two, being due to rupture of an aneurysm of the left anterior cerebral artery in one, due to rupture of an aneurysm of the middle cerebral artery in the other.

In all cases there was evidence of arterio-sclerosis, though the type of arterial disease, its chief incidence, and degree varied.

The cases are divided into two groups: Group I, in which diffuse hyperplastic sclerosis is a prominent lesion, and Group II, in which it is very slight or absent.

Group I, in which Diffuse Hyperplastic Sclerosis is Prominent.

Case No.	Sex.	Age.	Cor. Weight.	Large Vessels.	Kidneys.	Brain Lesion.
2	♂	53	19½	Some atheroma	Arterio-sclerotic	Intra-cerebral
14	♀	43	13½	Slight ,,	,, ,,	,,
18	♂	76	14½	Marked ,,	True chr. int. nephritis	Subarachnoid
25	♂	67	24½	,, ,,	,,	Intra-cerebral
10	♂	47	19½	Slight ,,	,,	,,
61	♂	36	32½	,, ,,	,,	,,

Group II, in which Diffuse Hyperplastic Sclerosis is Slight or Absent.

27	♂	51	11	Some atheroma	Arterio-sclerotic	Intra-cerebral
34	♂	47	14¾	,, ,,	,, ,,	,,
53	♀	65	17	Marked ,,	True chr. int. nephritis	Subarachnoid

In other respects than the degree of diffuse hyperplastic sclerosis and cardiac hypertrophy there is considerable overlap in the critical features of these cases. The sex incidence has already been mentioned. The age incidence of the first group varies between 36 and 76 years, an age period which on other grounds is considered true for this group of cases.

The age period for the second group begins at 47 years, the oldest case being 65 years. There is no doubt that these three cases do not express the

later extreme, for Sir Frederick Andrewes has shown that, if the proper correction for the number of persons living at each age period is made in the statistics, there is in fact an increasing liability to cerebral haemorrhage with increasing years.

There is a difference in the heart-weights in the two groups; the heart-weights in Group I average higher than those in Group II. Case 53 in Group II had cardiac hypertrophy due to myocardial disease. The post-mortem examination was done by Dr. T. H. G. Shore and described by him as a case of 'morbus cordis', though there was no valvular disease. There was, therefore, in this group no case of cardiac hypertrophy due to vascular as distinct from heart disease. Cardiac hypertrophy is characteristic on the other hand of Group I. The presence or absence of atheroma is no criterion. While I am in general agreement with J. F. Gaskell that the larger vessels tend to escape in diffuse hyperplastic sclerosis there is no doubt of marked atheroma of the aorta and larger trunks accompanying diffuse hyperplastic sclerosis of the intimate vasculature. There is no evidence in this research to support the view that the lesion 'spreads' from the intimate vasculature to the larger trunks. It is in my opinion but an example on a large scale of a characteristic feature of chronic vascular disease, namely, its apparently haphazard distribution. So far as these cases go there is no particular renal lesion associated with cerebral haemorrhage; chronic interstitial nephritis and arterio-sclerotic kidney occur in both groups; nor is the type of cerebral lesion characteristic of either group.

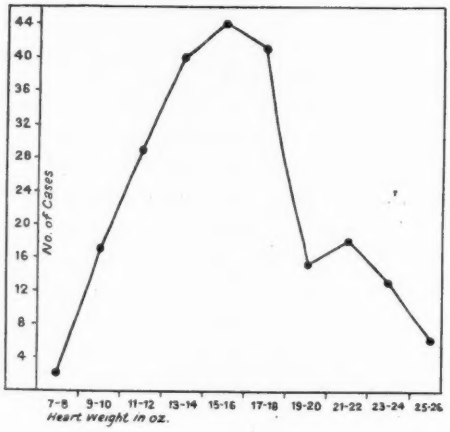
These cases are too few in number to allow of definite conclusions to be drawn from them; at the same time they are of interest in supporting the opinion based on the statistical evidence that follows, that cases of cerebral haemorrhage include two types of arterio-sclerosis, the one in which the arterial lesion is diffuse hyperplastic sclerosis, and the other in which the arterial lesion is patchy or local and probably often of the senile type. Just as there is no absolute distinction between senile and diffuse hyperplastic sclerosis, so there is no critical distinction between these two types of cerebral haemorrhage. The two types of cerebral haemorrhage conform to Sir Clifford Allbutt's hyperpietic and involutionary forms of arterio-sclerosis. Cerebral haemorrhage is clinical evidence of local arterial disease; it may be the first and last clinical expression of this disease; it may be additional evidence; but a raised blood-pressure or cardiac hypertrophy is the only adequate clinical evidence at present available of diffuse hyperplastic sclerosis.

Statistical evidence on cerebral haemorrhage. Sir Frederick Andrewes has already covered this ground in his analysis of the cases in fifteen of the twenty years which form the basis of my work. The main points have, therefore, been already made; at the same time the following charts support the conclusions arrived at above and complete the statistics already set out in the section on cardiac hypertrophy.

Chart XI, giving the heart-weights of all cases of cerebral haemorrhage, shows at a glance the predominance of cardiac hypertrophy in this condition.

The greatest number of cases die with a heart-weight of 15 to 16 oz. Of the 225 cases included in this graph the heart-weight was less than 15 oz. in 88 cases and over 15 oz. in 137.

Heart-weights of all Cases of Cerebral Haemorrhage. 1895–1914. Chart XI.



All Cases of Cerebral Haemorrhage. 1895–1914. Chart XII.

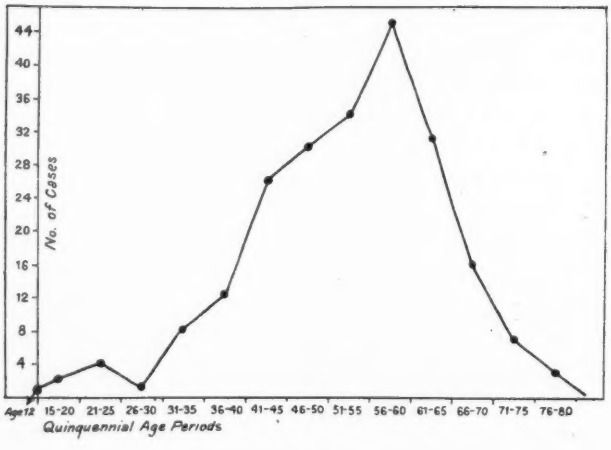


Chart XII shows the age incidence of cerebral haemorrhage with a maximum case mortality in the quinquennium 56–60 years, as compared with the maximum case mortality of cardiac hypertrophy in the quinquennium 61–65 years.

Six cases occurred before the age of 30, and the following précis of the post-mortem findings is given on account of the interest of these cases :

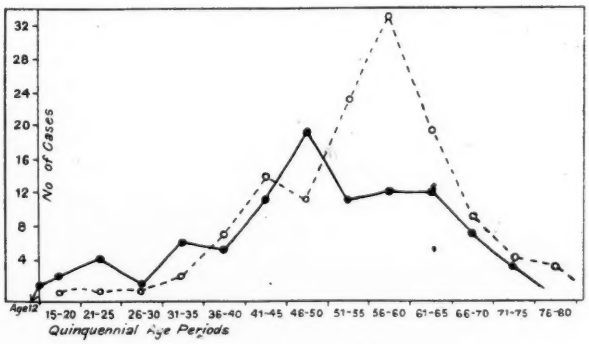
Remarks.	Cor. Weight.	Sex.	Age.	Lesion.	Aorta.	Kidneys.
? Cause	8 oz.	♂	12	Intra-cerebral	No atheroma	Normal
? Cause	7 oz.	♂	16	,,	,,	,,
Renal	12½ oz.	♂	19	Subarachnoid ruptured aneurysm	,,	Cystic chronic interstitial nephritis
Renal	13¾ oz.	♀	22	Subarachnoid ruptured aneurysm of antr. communicating artery	—	Contracted white kidney
W. R.	9½ oz.	♀	23	Subarachnoid ? aneurysm of basilar artery	—	—
? Cause	11½ oz.	♀	22	Intra-cerebral	Slight atheroma	Normal

Of the six cases two were associated with chronic renal disease, in one the Wassermann reaction was positive, in the remaining three no cause was found.

The irregularity in the upward curve in the quinquennium 41–45 years has already been discussed. If the cases are divided into two groups, namely, those in which the heart weighed up to 15 oz. inclusive and those in which it weighed more than 15 oz., a striking difference in the age mortality of the two groups is apparent. The graphs of these two groups are given in Chart XIII.

Cases of Cerebral Haemorrhage. 1895–1914. Chart XIII.

Ink line . . . cases with heart-weights up to 15 oz.
Dotted line . . „ „ „ above 15 oz.

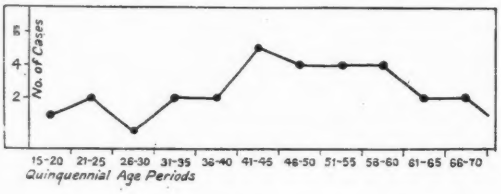


It is evident that between the ages of 50 and 65 some factor associated with cardiac hypertrophy, possibly raised blood-pressure in itself, becomes a determining factor in cerebral haemorrhage.

No light is thrown on the subject by isolating the cases of subarachnoid haemorrhage due to rupture of an aneurysm of a basal artery from the main

group. These cases, which are collected in Chart XIV, are curious in having no special age incidence, differing in this respect from aneurysm of the aorta and perhaps differing to this extent in their aetiology; H. Turnbull has suggested a congenital defect in these cases.

Chart XIV.



In conclusion, I may quote Sir Frederick Andrewes's figures for the association of cerebral haemorrhage and renal disease:

Extremely granular	2
Definitely „	120
Slightly „	22
Apparently normal	7

and his conclusion that 'in an overwhelming majority cerebral haemorrhage is associated with renal fibrosis'. It is the purpose of the following section to examine the nature of this renal fibrosis.

C. *Chronic Renal Disease in Relation to Diffuse Hyperplastic Sclerosis.*

(i) *General remarks.* It is impossible to deal with the subject of arterio-sclerosis without discussing chronic renal disease, for the two conditions are so often simultaneously present and the connexion between the two is one of the unsolved problems of medicine. The subject of chronic renal disease is of two-fold importance on account of its close association with arterio-sclerosis, and because its pathology throws light on the pathogenesis of arterio-sclerosis. It seemed at first unlikely that a subject in itself so complex, as is chronic renal disease, would throw a clear light on arterial disease; it seemed almost comparable to explaining X in terms of Y when both are unknown functions.

The subject is difficult, and Sir Clifford Allbutt speaks of the relation of arterio-sclerosis to kidney disease as one of the most baffling in pathology; Aschoff introduces his chapter on nephritis with the remark that it belongs without doubt to the 'am wenigsten geklärten' chapters in the whole of medicine; Osler summarizes the subject as follows: 'The relation between the arterial and kidney lesions has been much discussed, some regarding the arterial degeneration as secondary, others as primary. There are two groups of cases, one in which the arterio-sclerosis is the first change, and the other in which it is secondary to a primary affection of the kidneys.'

It is proposed to approach the problem from its histological aspect and examine specimens of chronic renal disease for signs of active inflammation.

In all kidneys extensively diseased I found evidence of active inflammation, and in all cases in which during life there were definite symptoms of renal disease there has been found post-mortem histological evidence of active inflammation in the kidneys.

The fact observed is the presence of active inflammation in extensively diseased kidneys. The conclusion drawn from this fact is that the underlying process in the production of these lesions is one of active inflammation. The corollary to this conclusion is no less important. In the first place, because renal arterio-sclerosis is commonly associated with chronic renal disease, it is additional evidence that the main process underlying the production of arterio-sclerosis is one of active inflammation.

In the second place, the question as to whether arterio-sclerosis produces chronic renal disease (and its inverse proposition that chronic renal disease causes arterio-sclerosis) becomes a matter of very secondary importance. In fact as a causative sequence in the production of a progressive lesion I doubt the validity of either proposition. My thesis may be alternatively stated thus: A pathogenic factor simultaneously causes both renal and vascular lesions, a varying incidence on renal or vascular tissue accounts for the unequal change in these tissues in different cases.

The present-day views on chronic renal disease are not crystallized. They are in general terms a compromise between the views expressed by Fagge and those expressed by Aschoff, the former a clinician and the latter a pathologist; hence the diversity in the modern view.

The problem centres round cirrhosis of the kidney, and in particular round that form of cirrhosis that is commonest between the ages of 40 to 60, and rarely, if ever, found below the age of 30. The synonyms given by Fagge (22, p. 492) are: 'Chronic interstitial nephritis—red granular atrophy—granular degeneration, producing the small red kidney of Bright—chronic gouty nephritis; Fr. Maladie de Bright, forme chronique aux reins ratatinés; Germ. Schrumpfniere'.

After discussing certain aspects of its aetiology, and in particular the view held by 'some German pathologists' that the primary change is glomerular and dependent upon an arteritis obliterans affecting the smaller branches of the renal artery in the cortex, Fagge summarizes his views in these words: 'A study of the early stages of the disease makes it, however, more likely that it begins as a subacute inflammation. In response to repeated but slight irritation, leucocytes are exuded between the tubules, and gradually form a granulation tissue which closely contracts, squeezing the tubules, destroying their epithelium, and thus reproducing Virchow's type of chronic interstitial inflammation with cicatrization, fibrosis, and contraction, which we have seen exemplified in sclerosis of the cord, fibroid pneumonia, and cirrhosis of the liver' (*loc. cit.*, p. 496).

Aschoff's views are given in his discussion of the sequelae of acute interstitial nephritis (*loc. cit.*, p. 467). He holds that most are fatal, and that those which

recover lead to some form of scarred or contracted kidney, though it is as yet uncertain for which form of contracted kidney a primary acute interstitial nephritis is responsible. 'Nur mit Wahrscheinlichkeit kann man sowohl nach der klinischen Erfahrung wie auch nach dem anatomischen Befund gewisse Fälle von sogenannter genuiner Schrumpfniere oder sogenannte Granularatrophie auf die interstitielle Nephritis zurückführen. Für die Mehrzahl der Fälle von genuiner Schrumpfniere fehlt aber der Beweis eines solchen Zusammenhanges, und die Pathogenese ist in einer besonderen Gefässveränderung zu suchen, deren letzte Ursache unbekannt ist.' In short, according to Aschoff, most cases of interstitial nephritis are primary vascular. J. F. Gaskell (*loc. cit.*, p. 289) takes a more extreme view: 'As far at any rate as the present observations are concerned, there is no evidence that acute interstitial nephritis leads to a chronic form of kidney change. . . . Professor Aschoff records in his text-book the belief that "genuine Schrumpfniere", which will be discussed later, may have its origin in this form. The evidence to be given later, however, tends rather to the conclusion that "genuine Schrumpfniere" has, as Jores suggests, its origin in a primary disease of the small arteries.' Gaskell's views have found general acceptance among those to whom they are known.

The aetiology of certain forms of renal disease in which chronic interstitial inflammation occurs is well known; for example, ascending infections of the kidney and tuberculous disease of the kidneys. These are excluded from the group called chronic interstitial nephritis; neither is the fibrotic form of chronic parenchymatous nephritis included in this group.

(ii) *Chronic interstitial inflammation.* There seems to be no particular reason for treating chronic interstitial inflammation of the kidney on different lines to those applied to the consideration of chronic interstitial inflammation in other organs. It is to be expected that the same aetiological factors will to an extent hold good in respect of chronic interstitial nephritis as in respect of chronic interstitial myocarditis, pancreatitis, mastitis, and cirrhosis of the liver. Chronic interstitial inflammation of these other organs is not explained in terms of obliterative endarteritis, and the arteriole distribution does not offer a sufficient explanation of the different interpretation applied. It is generally taught that the heart-muscle is supplied by end-arteries, and though arteriole obliteration is rare in the heart it might have been expected that some forms of interstitial myocarditis would have been interpreted in terms of arteriole lesion. *Per contra*, the spleen, an organ also supplied by end-arteries, does not suffer interstitial inflammation as a result of obliterative changes in its intimate vasculature.

A priori considerations are in fact in favour of Fagge's view already quoted, in which renal sclerosis is compared on equal terms with spinal, pulmonary, and hepatic sclerosis.

A distinction between active inflammation and replacement fibrosis is to be noted. Interstitial reaction occurs in both—that is to say, a small-cell infiltration followed by fibrosis. The difference between the two conditions lies in the fact that in the latter nobler tissue elements undergo degeneration or atrophy, while

in the former they may respond by proliferation to the insult of the pathogenic factor. The small-cell infiltration is more intense in the former, the fibrous connective tissue production more intense in the latter.

The essential criteria of active inflammation in the kidneys are to be found in the microscopical study of damaged organs. Clinical criteria are sufficient for the broad distinction of groups of cases, but are insufficient too frequently in the accurate diagnosis of single cases. The differential diagnosis of chronic nephritis and cardiac kidney may be extremely difficult, and there is no accepted clinical distinction between chronic interstitial nephritis and arterio-sclerotic kidney. There is not even a unanimous opinion on the clinical diagnosis of the several forms of so-called 'primary chronic inflammatory kidneys', the so-called 'white kidneys'. The clinical diagnosis does not always become simpler as the lesion develops, and in its last stages the differential diagnosis of uraemia and cerebral haemorrhage may be impossible. Clinical observations cannot therefore be relied on to supply the criteria for the absolute diagnosis of chronic renal disease or the classification of its types.

Macroscopic appearance of kidneys *post mortem* is equally unreliable. Granularity is but evidence of fibrosis and, *caeteris paribus*, colour is only determined by blood content of the organ, while size is in most cases a balance of fibrosis, blood content, and oedema. As long, therefore, as kidney diseases are classified according to their naked-eye post-mortem appearance there will be confusion in nomenclature and in classification.

More recently an attempt is being made to diagnose and classify renal disease by biochemical methods. Considerable success has already been achieved, but until the various changes in structure in renal disease are accurately realized, research on these lines must be limited.

It is in the recognition of changes in structure and the correlation of these changes with alterations in function that the surest advances in medicine have been made in the past. Since, however, naked-eye post-mortem appearances have proved insufficient, it must be in more detailed histological study that further progress in the knowledge of kidney disease lies.

In order to obtain histological criteria of active inflammation of the kidney, I have examined cases of acute nephritis in which it is accepted that the pathogenic factor is infective and its effect on kidney tissue that of active inflammation. I accept the dualist conception of renal disease and refer to parenchymatous and interstitial nephritis as two distinct forms; at the same time it is recognized that no microscopical specimen reveals the lesion limited to parenchymatous or interstitial tissue; the distinction is justified, however, in the greater incidence of the lesion on the one type of tissue than on the other. In cases that present difficulty in making a distinction the term diffuse nephritis is used.

(iii) *Several forms of renal disease examined with reference to the presence of signs of 'active inflammation' and coincident vascular lesions.*

(a) *Acute nephritis.*

(1) Acute parenchymatous nephritis (syn. tubular nephritis (Fagge), acute Bright's disease (Osler), glomerulo-tubular nephritis (Aschoff)).

(2) Focal embolic nephritis (Libman).

(3) Acute suppurative nephritis (haematogenous form of Aschoff).

(4) Acute interstitial nephritis.

(α) Ascending suppurative nephritis (Aschoff).

(β) Tuberculous pyonephrosis.

A single example will be given of each type named above. The list is not intended to include all forms of acute nephritis. Attention is focused on the lesions of the glomeruli and the intimate vasculature. Since all the above conditions are known to be of infective origin it is held that the changes in structure of glomeruli and intimate vasculature are those of active inflammation; since the processes are acute it is further held that the lesions in the glomeruli and intimate vasculature result from a pathogenic agent common to both, and that the vascular lesion neither causes the glomerular lesion, nor does the glomerular lesion cause the vascular lesion.

(1) *Acute parenchymatous nephritis* (Glomerulo-tubular of Aschoff). My series does not include a case of this form of renal lesion, but Dr. J. H. Drysdale has kindly given me his specimens of acute nephritis prepared in the laboratory of Professor Weichselbaum, of Vienna. The following description is based on this specimen, which is a typical scarlet-fever kidney of the glomerulo-tubular type. The glomerular lesion is diffuse; the majority of glomeruli show signs of inflammation to greater or less extent; most glomeruli show marked inflammatory change, the outstanding feature of which is a proliferation of the cells of Bowman's capsule. Owing to the method of preparation (paraffin embedded and xylol cleared) the hyaline exudate into the intercapsular space is not apparent, having been lost in the making of the section. There is a heaping up of proliferated epithelial cells in the intercapsular space, and an examination of many glomeruli leads to the conclusion that these cells are in some cases derived from proliferation of the visceral layer of Bowman's capsule, and in some from the parietal layer. In other glomeruli both layers of epithelial cells, that form respectively the visceral and parietal layers of Bowman's capsule, are involved. Where the potential space between the two layers of Bowman's capsule, the intercapsular space, is still extant it is easy to determine to which layer the proliferated cells belong; in other glomeruli the space is in part or whole obliterated, and in these it is difficult to ascertain the origin of the proliferated cells. In general, proliferation of the parietal layer tends to be more uniform in the circumference of the glomerulus, resulting in the formation of a cellular thickening of the

capsule in concentric rings made up of proliferated epithelial cells, whereas proliferation of the visceral layer tends to be more local and typically gives rise to local accumulations of proliferated cells, which may form small masses of four or five cells bunched together, or more typically form crescent-shaped groups of cells. In the particular section described, red blood corpuscles are not seen in the intercapsular space, nor is it unlikely that some of the proliferated cells are in fact leucocytes or wandering connective tissue cells. The glomerular tuft may be relatively intact, though there is in the majority evidence of cellular proliferation in the tuft and increase in the apparent number of nuclei. Degenerative changes are present in some of the glomeruli in the form of a hyaline degeneration of the glomerular tuft (partial) or of the proliferated epithelial cells.

(2) *Focal embolic nephritis* (Libman). The same lesion of the capsule is present as has already been described in scarlatina nephritis. The visceral layer proliferation is the most marked feature; it will, in future, be referred to as 'endoglomerulitis'. The parietal layer is likewise involved, and there is also a pericapsular small-cell infiltration. In addition there is a local hyaline degeneration of the glomerular tuft due to focal necrosis of a part of the capillary nexus. In this also it is no matter whether this focal capillary change is the result of infarction or local necrosis; the main point is the hyaline swelling and degeneration of a part of the capillary loop resulting from an infective condition. This lesion, focal embolic nephritis, in a single glomerulus expresses my thesis in the simultaneous affection of the intimate vasculature of the kidney (the capillary nexus in the glomerular tuft) and of the kidney parenchyma (the epithelial cells of Bowman's capsule) resulting from the insult of a pathogenic agent known to be of an infective (bacterial) nature.

(3) *Acute suppurative nephritis.* Case 72. This specimen was also taken from a case of malignant endocarditis and shows a similar glomerular lesion to the last. It differs from the last section in that (1) the glomerular inflammation is diffuse, the great majority of glomeruli being affected, and (2) the kidney is studded with miliary abscesses. This specimen illustrates a diffuse glomerulitis due to an acute bacterial infection.

There are certain differences in these specimens by which they may be distinguished histologically, but they are alike in the essential lesion, which is an active glomerulitis. The type of glomerulitis shown by the specimens is an 'endoglomerulitis'. The characteristic features of acute or recent endoglomerulitis are: (*a*) Involvement of the tuft in hyaline degeneration and swelling of the capillary nexus in which the earliest stage of fatty degeneration is occasionally seen; alternatively, a proliferation of the cells of the tuft. (*b*) Involvement of the capsule of the tuft, either of the visceral layer which covers the capillary nexus or of the parietal layer which is separated by a potential space from the visceral layer. In either event—and both are frequently present together in one glomerulus—the epithelial cells which form these two layers proliferate, and are heaped up in the intercapsular space in small masses or crescent form. More commonly, when the parietal layer is involved the proliferated cells are arranged in the form

of concentric rings around and continuous with the capsule of which they are a part.

(4) *Acute interstitial nephritis.* This term is used to describe the condition in which the inflammatory reaction is more evident in the interstitial tissue than in the parenchyma.

(*a*) *Type of ascending suppurative nephritis* (Aschoff). Case No. 12. E. S., female, aged 44, was admitted January 23, 1919, to Martha Ward, care of Dr. W. S. A. Griffith, complaining of a vesico-vaginal fistula. A plastic operation was performed February 3, 1919, and a self-retaining catheter was inserted. This was removed February 12, when the urine was noted to contain a trace of albumin and a few pus cells. On the 20th the fistula was still present; the temperature rose on this day to 102° F., and there was complaint of great pain in the left loin. Pyuria developed. On the 27th *Bacillus coli* and staphylococci were cultivated from the urine; on March 7 streptococci were isolated from the urine and a vaccine was prepared. The patient died of septicaemia on March 15. There were no symptoms of uraemia, viz. headache, vomiting, dyspnoea, or convulsions. *Past history*: five years ago the uterus was removed on account of a tumour.

Post mortem: well-nourished body, well developed.

Lungs: Rt./Lt., 21/12 oz. Oedema of lungs with massive collapse at left base; recent adhesions of right and left pleurae. *Heart*: 8¾ oz. Valves natural. No pericarditis. Heart-muscle pale and flabby. A little fatty intimal change at base of aorta, the large vessels being otherwise natural. *Brain, liver, spleen,* and *intestines* showed no point of special interest. *Kidneys*: Right, 8½ oz. Swollen, pale, and mottled, with lack of distinction between cortex and medulla. Minute metastatic abscesses in pyramids. Left, 5½ oz.; the kidney was a bag of pus with relatively little renal tissue left. It lay in a purulent mass involving the left suprarenal gland and the tail of the pancreas. *Bladder*: Acute cystitis. Urea in cerebro-spinal fluid. P.M. = 0·21 per cent.

Post-mortem diagnosis. Septicaemia; acute cystitis, ascending infection of the left kidney leading to pyelonephrosis and perinephric abscess. Metastatic abscesses in the right kidney.

Histological examination. The following organs showed no evidence of vascular disease: spinal cord, pons, medulla oblongata, mid-brain, liver, heart, abdominal muscle, stomach, lung, and suprarenal. The vertebral artery showed slight intimal thickening and the aorta a slight intimal fatty change. *Kidneys*: Right kidney showed in general a condition of cloudy swelling and desquamation of tubular epithelium. Minute metastatic abscesses were seen in the pyramids, and some glomeruli in their immediate neighbourhood showed acute glomerulitis with hyaline degeneration in the tuft of the affected glomeruli. Apart from this focal capillary lesion there was no change in the intimate vasculature of the kidney. Left kidney showed a diffuse fibrosis with marked small-cell infiltration, from which lesion one part of the renal tissue escaped and remained relatively normal. In that part of the renal tissue chiefly affected by inflammatory change the glomeruli had undergone hyaline degeneration with varying degree of reactive proliferation of Bowman's capsule; in some there was periglomerulitis, and in other glomeruli there was both endoglomerulitis and periglomerulitis. The whole picture, both histologically and macroscopically, was one of active inflammation.

The arterial change is of interest. In the case of the larger arteries, the first branches of the main divisions of the renal artery (commonly called the arterial arches, though these arches do not exist according to Gross), there was intimal hyperplasia of a definite though not very marked degree, without fatty degeneration. There was in addition adventitial thickening. The media was intact without small-cell infiltration or degenerative changes, neither was there muscular hyper-

trophy. The intermediate and smaller arteries showed marked intimal hyperplasia, and in addition there was occasional fatty degeneration of the media. The arterioles, whose media was two to three muscle cells in thickness, in general showed a hyaline degeneration of a thickened intima with patches in their length of fatty intimal degeneration having a uniform circular distribution. The distribution of this change in the length of the arterioles was traced in serial sections, of which 140 consecutive specimens were mounted in series, each cut 30 μ thick. So far as my observations go the hyaline swelling of the intima of affected arterioles was continuous, while the fatty change was partial in its distribution along the length of the vessel though complete in its circumference. Arterioles which were traced to degenerated glomeruli showed this fatty degeneration.

In those areas in which the inflammatory process was most advanced the arterioles were not seen; on the other hand, in the relatively unaffected region there was no arteriole lesion, and in so far as arterioles were traced to normal glomeruli these arterioles were normal.

In short, there was a vascular lesion of the diffuse hyperplastic sclerosis type. This vascular lesion was limited to the kidney affected by interstitial inflammation, and in that kidney was limited as regards arteriole change to the affected part. There was thus the closest association between the renal and vascular lesion, and it is concluded that the vascular lesion was the result of active inflammation.

In the spleen a few arterioles showed the typical intimal change with fatty obliteration of the lumen. The second size arteries did not show intimal thickening.

The absence of diffuse hyperplastic sclerosis in other organs of the body examined (with the exception of the slight vascular lesion in the spleen), particularly its absence from the right kidney, demonstrated the local condition of the left kidney as the cause of the change in the intimate vasculature of that organ.

This case is brought forward as evidence of the view that diffuse hyperplastic sclerosis is an active inflammatory process. The bacteriological evidence obtained during life pointed to a pyogenic infection, namely, *B. coli* and streptococcus infection.

This case is of additional interest in that it gives an indication of the time taken for development of the arterial lesion. The operation was presumed to date the first infection; the first indication of this infection was nine days later, when the urine was found to contain a 'trace of albumin and a few pus cells'. General reaction to infection took place seventeen days after operation and was marked by fever rising to 102° F. On the same day the patient first complained of pain in the left loin. Death occurred thirty-two days after the presumed original infection. It is quite reasonable to assume that the renal infection was of longer standing, but the evidence available pointed to its total duration being thirty-two days. It is therefore concluded that this intimal hyperplasia took place within a period of thirty-two days.

(β) *Tuberculous pyonephrosis.* Case No. 51. The specimen to be described was removed by operation by Mr. Girling Ball, to whom I am indebted for the specimen. It was an advanced specimen of tuberculous pyonephrosis. The histological picture was typical of the condition showing massive small-cell infiltration and accompanying fibrosis with degeneration and atrophy of renal parenchyma. The section showed many giant cells. The glomeruli were largely destroyed, many showed advanced degrees of hyaline and fibroid degeneration, others less affected showed a proliferation of the parietal layer of Bowman's capsule. This thickening of Bowman's capsule is capable of interpretation in terms of fibrous connective tissue proliferation, since it was not very cellular. The point is, however, immaterial, as there was other conclusive evidence of the active inflammatory nature of the lesion. There was advanced intimal hyperplasia of the second and third size arteries. No fatty obliteration of arterioles was seen. The intimal hyperplasia was, in general, of the diffuse hyperplastic sclerosis type, but several arteries were of particular interest in showing the acute form of endarteritis. There is no doubt, therefore, that the arterial lesion was of the type of active inflammation.

In these cases there is transparent evidence of the activity of an active inflammatory process. The critical evidence of active inflammation is a proliferation of the cells forming the visceral layer of Bowman's capsule, endoglomerulitis, and (or) proliferation of the cells forming the parietal layer of Bowman's capsule. In addition a marked small-cell infiltration is a characteristic feature of the picture. Though it is possible to explain the small-cell infiltration as secondary to tissue necrosis resulting from sudden obliteration of arterioles (Aschoff), an alternative explanation is more likely when a proliferation of the epithelial cells of Bowman's capsule takes place. I hold that proliferation of the epithelial cells of Bowman's capsule is unequivocal evidence of the process of active inflammation. In these specimens various degrees of arterial change are seen. In one case it was limited to a hyaline degeneration of the capillary nexus in the glomerular tuft; in a second case there was, in addition, the typical intimal proliferation seen in the second and third size arteries of diffuse hyperplastic sclerosis; in a third case this intimal proliferation had the appearance in some arteries of acute endarteritis; in a fourth case the complete picture of diffuse hyperplastic sclerosis was present.

These cases are evidence in favour of the view that both renal and vascular lesions are direct results of a single cause, the cause being bacterial infection, and the underlying pathological process one of active inflammation.

(b) *Chronic parenchymatous nephritis.* We now pass to a group of kidney lesions which are as certainly active inflammatory as the last group; they are less certainly bacterial in origin, and the lesion diffuse hyperplastic sclerosis is a more prominent feature of the histological picture. The kidney lesion is diffuse; the glomerular lesion is of the same nature as in the last group; namely, an endo- or peri-glomerulitis.

Case No. 39. *Chronic parenchymatous nephritis.* Type 1 (contracting white kidney in a clinical sense). K. I., female, aged 31, admitted to Surgery Ward under the care of Mr. Sydney Scott, complaining of a purulent discharge from the right ear and headache. She gave a three days' history of acute suppurative otitis media.

On admission there was some tenderness over the right mastoid region, and two days after admission definite mastoid tenderness developed. There was marked pyorrhoea alveolaris and bleeding gums. The headache was of the basal ear type; there was no oedema of the face, slight oedema of the shins. Urine contained 1·3 per cent. albumin (Esbach) and pus cells. Bacteriological examination of a catheter specimen of urine was negative. Two blood-culture examinations were negative. In consultation with Sir Archibald Garrod, Mr. Scott decided that the renal condition rendered operative treatment impossible. The temperature remained raised and the clinical picture was that of septicaemia with frequent rigors. Death occurred from septicaemia ten days after admission.

In 1914 the patient was for two months under treatment in an infirmary with general oedema and signs and symptoms (the details of which were not recorded) which led the House Surgeon, Mr. Barnes, to a clear diagnosis of chronic nephritis. There was no past history for ear trouble.

Post-mortem report:

The body of a small, poorly nourished woman. Right suppurative otitis media, lateral sinus normal.

Heart 12 oz., no valvular lesion, left ventricle hypertrophy.

Aorta, fatty streaks; no sclerosis. *Spleen*, firm and tough, 5 oz. *Brain* and *lungs* described as normal. *Liver*, 49 oz., fatty. *Kidneys*: Rt./Lt., 3/2 oz., not adherent to perirenal tissues. Both very small and pale in colour, surface markedly granular, no venae stellatae; resistant on section, cut surface pale, cortex and medulla much narrowed, pelvic fat increased, arteries gaping in slight degree; capsule thickened and stripped with difficulty.

This was a typical description of the so-called small white kidney, which was simply an advanced renal sclerosis. The left ventricle was hypertrophied, but the weight of the heart showed that the hypertrophy was of inconsiderable degree. The main vascular trunks showed no marked arterio-sclerotic change.

Histological examination. Characteristic picture of diffuse parenchymatous nephritis with marked sclerosis. The glomerular affection was diffuse and the glomeruli presented complete evidence of active inflammation. There was marked tubular change. At the same time there was advanced interstitial fibrosis with small-cell infiltration, *and simultaneously an advanced degree of diffuse hyperplastic sclerosis limited to the intimate vasculature of the kidney.* Histologically the lesion may be described as a chronic diffuse nephritis.

In detail the glomeruli were all involved to greater or less extent in the inflammatory lesion. Many typical glomeruli showed proliferation of the visceral layer of Bowman's capsule; in some there was also proliferation of the parietal layer. There was obvious adhesion in many glomeruli of the tuft to the capsule; see Fig. 8, Plate 6. In general the tuft showed advanced hyaline degeneration of the capillary endothelium with varying degree of fatty degeneration, marked diminution of the number of nuclei, proceeding in many to complete degeneration of the tuft and fibrosis. There was marked atrophy of the renal tubules, the epithelium being flattened, the lumen increased; the cell nuclei stained poorly in many parts. Occasional evidence of hypertrophy of tubule epithelium. There was considerable dilatation of collecting tubules and loops of Henle. The whole renal parenchyma was very much reduced in size, and its normal arrangement disordered. The interstitial tissue showed nearly equally striking changes. There was marked capsulitis, as shown by thickening and vascularization of the capsule with wedges of fibrous connective tissue and small-cell infiltration spreading into the substance of the kidney from the capsule. The intimate vasculature showed the typical lesion of diffuse hyperplastic sclerosis in advanced degree. The fatty degeneration of the intima of arterioles leading to apparent obliteration of the lumen was a prominent feature, while the second and third size arteries showed extreme hyperplastic thickening of the intima without fatty degenerative change. In several arteries this intimal hyperplasia had led to almost complete obliteration of the arterial lumen. Several other organs of the body were examined, and in none of them was there any arterial lesion, namely, spleen, liver, medulla (two parts of same), heart, lungs, abdominal muscle. The radial artery was normal; the aorta showed slight fatty intimal degeneration without hyperplasia; the renal artery showed a similar condition. The carotid artery showed slight intimal thickening with a little fatty degeneration in the intima.

Discussion. The arterial change is limited to the kidney in so far as the intimate vasculature of the organs is concerned. The absence of arterial change in the spleen is important, and shows that this is not a case of diffuse hyperplastic sclerosis appearing as a coincidence in a case of chronic nephritis. The main vessels have to all intents and purposes escaped, as is often the case in diffuse hyperplastic sclerosis. The renal lesion is inflammatory, and the glomeruli show evidence of active inflammatory changes; these are in part old, as shown in the adhesion of the tuft to the capsule. The age of these changes is given by the clinical history of nephritis lasting two months and occurring five years before

death. The case was clinically one of chronic parenchymatous nephritis; the history of oedema five years before places this specimen in the class of secondary contracting kidneys, the sclerotic stage of a large white kidney, possibly a sequela of acute nephritis. No past history of scarlet fever or history sufficient to indicate the cause of the nephritis was obtained. The arterial change was exceedingly marked, and in this fact it stands out as an important exception to Gaskell's statement that arterial lesions in chronic parenchymatous nephritis and senile kidney are less evident than in the 'reine Schrumpfniere' of Aschoff.

I maintain that this case reopens the question of the aetiology of diffuse hyperplastic sclerosis in association with renal disease, because, in that an advanced degree of arterio-sclerosis is present in an active inflammatory condition, it raises the question as to how far the vascular lesion in other cases of chronic renal disease is the result of an active inflammatory process.

It must be admitted that in this case the renal lesion is primary, and as regards the vascular there are two alternative views, (*a*) that it is also primary and inflammatory, or (*b*) that it is secondary and involutionary. If the latter view is correct an additional factor must be introduced to explain the fatty arteriole change—that is to say, a degenerative process such as would result from a toxic cause. If this were due to failure of renal function it is difficult to explain the absence of sclerosis in the vasculature of other organs.

The simplest view is to regard both the renal and vascular changes as the result of the same *materies morbi*, the underlying process being active inflammation. This case, therefore, supports the view that arterio-sclerosis of the diffuse hyperplastic type is an active inflammatory process. The case has a second important bearing in illustrating the fact that advanced renal sclerosis is not necessarily associated with marked left ventricle hypertrophy. Other cases have been given in support of the view that renal disease *per se* is not the cause of marked left ventricle hypertrophy.

It has already been shown that there is a close association between marked left ventricle hypertrophy and raised blood-pressure. The evidence in favour of this association appears to justify the conclusion that there was not a persistently raised blood-pressure in the case now under review, and to that extent it excludes the possibility of raised tension having been more than a trivial factor in the production of arterio-sclerosis in this case, a view that is further supported by the limitation of the arterio-sclerotic process to the renal vasculature. This aspect of the case is of interest in that the association of arterio-sclerosis with chronic renal disease is usually discussed from the point of view of raised blood-pressure.

In short, the case emphasizes a distinct aspect of the association of chronic nephritis and diffuse hyperplastic sclerosis, for it receives its simplest interpretation in terms of an active inflammatory process occurring simultaneously in vessels and secreting tissue, the result of a single cause.

Contracted white kidney. In the use of this term a distinction is made from contracting white kidney on purely clinical grounds. The two kidneys are alike in being smaller than normal, granular, and pale. The cases differ in the absence

of a history of renal oedema in the contracted white in distinction to its presence in the contracting white. A different aetiology for the two conditions is presumed, though it is not yet established that they are in fact different.

Case No. 4. C. G., female, aged 39, admitted July 1, 1914, care of Dr. H. H. Tooth, complaining of headache, vomiting, dyspnoea, and increasing weakness. H.P.C.: For the past year had suffered from increasing headaches and more recently had complained of vomiting and weakness. P.H.: None of scarlet fever. Fair health until miscarriage in January, 1914. Tonsillitis February, 1914. P.C.: A.B., in space 6, anterior axillary line. No murmur. Radial artery thickened and tortuous. B.P., 215 mm. Hg. Albuminuric retinitis. Oedema of legs only. Urine scanty, loaded with albumin; contained pus cells and casts, no R.B.C. C.S.F. urea 0·6 per cent. Death from uraemia.

Post-mortem, 10.7.14: Chronic nephritis, contracting kidney. Hypertrophy and dilatation of heart. Arterial degeneration. *Heart*, 19 oz. Marked hypertrophy of left ventricle. *Aorta*, plaques of atheroma. Head and neck not examined. *Kidneys*: Right, 5½ oz. Left, 2 oz., small and lobulated. Both kidneys coarsely granular, mottled pink and red with punctate haemorrhagic projections about 1 mm. across. Cortex much reduced, streaked red and white, punctate haemorrhages in places. Pelvis normal. Capsule of both organs adherent.

Histology. Kidneys: Type, fibrotic chronic parenchymatous nephritis. Diffuse affection of glomeruli with typical endoglomerulitis; some show fibrous periglomerular thickening. Marked interstitial inflammation with massive small-cell infiltration. Marked tubular damage. Typical diffuse hyperplastic sclerosis, not a prominent feature, in part owing to marked parenchymatous change. Intimal thickening of second size arteries marked. In general normal structure of renal tissue destroyed.

Other organs of which the intimate vasculature was examined and found normal: spleen, heart, pancreas, and suprarenal.

Aorta: slight intimal thickening and fatty change in intima. *Radial artery*: minimal intimal thickening, otherwise normal.

Summary. A case of true chronic nephritis with which there is associated diffuse hyperplastic sclerosis limited to the intimate vasculature of the kidney. This case is comparable histologically to Case 39, and illustrates the limitation of the arterial lesion to the kidney. It differs clinically from Case 39 in the absence of a history of oedema or past nephritis, in the cardiac hypertrophy and raised blood-pressure.

Case No. 1. E. W., male, aged 29, admitted June 25, 1914, care of Sir Wilmot Herringham, complaining of vomiting, and semicomatose. H.P.C.: Was quite well until June 10, 1914, when before breakfast and shortly after getting up, his wife noticed drowsiness; the patient complained of faintness and giddiness. He vomited about a pint of green fluid. Vomiting recurred six times in the day, always preceded by nausea. B.O. very loose. Doctor called in, diagnosed bad attack of influenza. Since, had vomited six times daily, complained of headache and delirium but not unconscious. Complained of pain in left hypochrondrium, continuous and not relieved by vomiting. P.H.: Teetotaller and nothing to suggest V.D. P.C.: Almost comatose on admission, skin dry, vomiting. Pulse regular, artery very wiry. B.P., 150 mm. Hg. No hypertrophy of heart. Retinal vessels normal. W.R. negative. Urine 1,004 acid, 0·15 per cent. albumin. No blood: contained granular casts.

Sir Wilmot Herringham's note is as follows: 'Condition curious, more the diabetic type than anything else; no air-hunger, though when turning on to back occasional sobbing inspiration. Will do what he is told. Though not

asleep seems hardly conscious of his surroundings. He moves all his limbs. Quite continent.'

Post-mortem, 3.7.14: *Heart*, 10½ oz., by no means hypertrophied. Aorta, carotids, iliacs, and arteries at base of brain normal, with small plaques of nodular sclerosis in descending aorta (not markedly abnormal condition). *Right kidney* absent, though right suprarenal normal. Right ureter was present, being, however, much smaller than normal. It appeared to commence in connexion with some fibrous tissue on the right of first lumbar vertebra and could be traced down to the bladder. In its upper part it appeared impervious, but near the bladder it was found to have a minute lumen too small to admit a probe. The opening into the bladder was not found. *Left kidney*: 3¼ oz., very small, globular in shape and unduly mobile. Tough on section with much reduced cortex. Vessels not abnormally thickened to naked eye. Surface extremely granular. Mucous membrane of bladder not unduly thickened, bladder small. Urea C.S.F., P.M. 0·88 per cent.

Histology. Kidneys: Type chronic interstitial nephritis with parenchymatous change. Capsulitis marked and interstitial inflammation spreading into substance of cortex. Glomerular lesion partial, chiefly affected in regions of fibrosis, some glomeruli normal. Affected glomeruli showed endoglomerulitis and some showed periglomerulitis. Tubule dilatation and atrophy of epithelium; patchy fatty degeneration.

Second size arteries showed intimal thickening; occasional arterioles showed fatty obliteration of the lumen. The intimate vasculature of other organs was examined. Diffuse hyperplastic sclerosis was found in slight degree in the spleen and brain. It was absent in the liver, heart, and skeletal muscle.

Aorta: intimal thickening with slight fatty change; early fatty degeneration of media; ordinary patch of nodular sclerosis.

Summary. A case of contracted white kidney in which the total weight of kidney substance was 3¼ oz., in which there was no cardiac hypertrophy. The kidney lesion is of the true chronic interstitial nephritis type, being partial in its distribution through the organ.

The active inflammatory nature of the kidney lesion shows that it is primary and not secondary to arterial disease, and is evidence that the vascular lesion is active inflammatory.

Case No. 43. F. G., female, aged 46, admitted Aug. 13, 191?, care of Dr. Morley Fletcher, complaining of difficulty in passing urine, weakness, and shaking right leg. H.P.C.: Six weeks B.O. irregular. Marked irritation of skin of trunk and limbs with appearance of watery blisters, which after a few days became papules. About the same time ulceration of mouth and tongue with bleeding and epistaxis; recurrence of this bleeding two or three times.

Four weeks jumping and trembling of right leg, persisted since. Two weeks weak and confined to bed; two days difficulty in passing urine.

P.H.: For six years bilious attacks on and off and morning nausea. Summer, 1913, swelling and pain in hands, knees, ankles, and shoulders. October, 1913, all teeth extracted except three, severe attack at this time of oral sepsis; since then repeated attacks. F.H.: Married. No children. Amenorrhoea five years. P.C.: Sallow and very pale; face puffy. Mouth, ulceration of lips and tongue. Heart not hypertrophied, normal. B.P. 130 mm. Hg. Pulse 86, regular, good volume; artery thickened and tortuous. Heart sounds normal. Kidneys not palpable, not tender. Abdomen normal. P.R. normal. Few ecchymoses on upper and lower limbs. Fine tremor of fingers. Urine pale, turbid, 1,012. 0·17 per cent. albumin. No sugar. Many pus cells, few R.B.C. *B. coli* on culture.

Blood count. R.B.C. 2,140,000. Hb. 30 per cent., C.I. 0·6, W.B.C. 8,400. Further note reported persistent vomiting and anorexia. Death occurred suddenly, August 20.

Post-mortem, 21.8.19. Chronic parenchymatous nephritis; chronic peritonitis and perihepatitis; hypertrophy of heart, atrophy of kidneys. Head and neck not examined. Heart 13½ oz. Concentric hypertrophy of left ventricle; no dilatation; no valvular lesion. Aorta and blood-vessels normal. Chronic peritonitis with omental adhesions. Liver 44 oz., perihepatitis; section normal. Kidneys not adherent. Right 2¼ oz., left 1¼ oz. Hard, pale, shrunken, and fibrotic; capsule adherent. On section almost total absence of cortex. Surface very granular. Urea C.S.F., P.M. 0·55 per cent.

Histology. Very advanced interstitial nephritis with very marked capsulitis and new vascular channels in capsule which showed intimal thickening. Marked subcapsular small-cell infiltration. Whole kidney structure completely disorganized. Tubules showed atrophy and dilatation, patchy fatty degeneration. Glomerular lesion diffuse. Many showed advanced grades of hyaline degeneration and fibrosis. Many showed true periglomerulitis, the cellular proliferation of which showed hyaline degeneration and occasional fatty degeneration; other glomeruli showed true endoglomerulitis (viz. adhesion of glomerular tuft to capsule). Blood-vessels showed very advanced diffuse hyperplastic sclerosis. In the second size arteries there was marked intimal thickening with proliferation and splitting of the internal elastic lamina and apparent thickening of media. Arterioles showed typical fatty obliteration, not many thus affected, and occasionally associated fatty medial degeneration.

The intimate vasculature of the following organs was examined: Diffuse hyperplastic sclerosis was found in the spleen and was absent in the liver, heart, skeletal muscle, bladder, cervical and parotid glands. The second size arteries of the liver showed intimal thickening. Aorta, slight intimal thickening with fatty degeneration, radial artery normal except for one slight patch of intimal thickening. Renal artery showed slight intimal thickening and fatty degeneration.

Summary. A true chronic diffuse nephritis of the 'contracted white kidney' type, in which there is very marked arterio-sclerosis of the inflammatory type. A case in which the left ventricle hypertrophy was not marked and, being less than 15 oz., is absent by my standard.

Case No. 71. A. T., aged 26, admitted December 4, 1919, care of Sir Archibald Garrod, complaining of pain in neck and right groin, due to abscess deep in the right thigh. H.P.C.: For some months morning vomiting. For three to four weeks epistaxis. P.H.: 1905–1906 long illness due to osteomyelitis of right femur. Sequestra removed by Sir Anthony Bowlby in this hospital. Joined army as A 1 man, 1917; a fit when on service. Albumin found in urine. Several fits since. P.C.: Alabaster aspect. R.B.C. 1,700,000. Polymorphonuclear leucocytosis. W.B.C. 19,400. No glandular enlargement. Spleen not enlarged. Urine 750 c.c. in 24 hours. Pale, 1,012. Alb. + +. No casts. C.S.F. urea 0·47 per cent. Fundi normal. December 6, apathetic, air-hunger, and increasing drowsiness. Died 3.55 p.m. December 7.

Post-mortem, 8.12.19. No oedema of skin. Slight oedema arachnoid. Brain arteries normal. Heart 16 oz., considerable hypertrophy left ventricle. Valves normal; myocardium normal. Aorta normal. Liver 65 oz. Spleen 8 oz. Kidneys, right 3 oz., left 4 oz. Both very small and adherent to perirenal tissues. Firm and pale on section; cut surface uniform pale on section. Capsule adherent and leaves finely granular surface. Cortex narrowed. Vessels in boundary zone unduly prominent; marked increase in peripelvic fat. Granules on surface of organ after stripping capsule pale in colour, not unlike tubercles with darker tissue between them.

Histology. Type chronic diffuse nephritis complicated by advanced amyloid disease. Marked capsulitis with small-cell infiltration and advanced interstitial fibrosis. Diffuse affection of glomeruli showing typical endoglomerulitis and in some cases periglomerulitis, which was chiefly of the nature of fibrous connective tissue thickening. Amyloid degeneration very advanced. Usual tubule damage.

Typical diffuse hyperplastic sclerosis except that its distribution both as regards arterioles and arteries was somewhat irregular.

The intimate vasculature of the following organs was examined: Slight diffuse hyperplastic sclerosis was found in the spleen; it was absent in the brain, liver, heart, lung, and suprarenal gland. Amyloid disease was also present in the spleen, brain, liver, and heart; it was not found in the lung or suprarenal.

Summary. A case of true nephritis associated with amyloid disease and diffuse hyperplastic sclerosis. It illustrates the same points as the preceding cases and resembles Case No. 4 in having cardiac hypertrophy.

Clinically these cases are alike in the absence of a history of renal oedema, in presenting characteristic symptoms of kidney disease, and in the fact that death was due to uraemia. *Post mortem* there was advanced kidney disease in each case, and though the histological picture varies it is characteristic of active inflammation of the renal parenchyma. The vascular lesion in each case was typical of diffuse hyperplastic sclerosis, and in Cases No. 43 and 71 it was a prominent feature. These cases, therefore, belong to the main group of diseased kidneys characterized by the active inflammatory nature of the kidney lesion, a group which is evidence of the active inflammatory nature of diffuse hyperplastic sclerosis. In these cases of true chronic nephritis the glomerular lesion is typically diffuse.

We now pass to the consideration of a group of chronic renal lesions in which the glomerular lesion is typically partial, namely, so-called 'chronic interstitial nephritis', using this term in its old-fashioned sense as used by Fagge.

(c) '*Chronic interstitial nephritis,' so called.* Clinically this type of kidney disease is recognized as a type of chronic renal fibrosis rarely occurring before the age of 35 and commonly occurring after the age of 40. It is closely associated with arterio-sclerosis. Death occurs from cerebral haemorrhage, heart failure, uraemia, or intercurrent disease. An extreme view places all kidneys included under this heading in the group of renal lesions that are secondary to primary vascular disease. Two forms are recognized by those who take this view, namely, the senile arterio-sclerotic kidney and Aschoff's 'reine Schrumpfniere'. In these kidneys the parenchymatous lesion is not a marked feature of the histological picture, whereas the vascular lesion is.

The histological criterion by which I judge any kidney as belonging to this group of 'so-called chronic interstitial nephritis' is the distribution of the lesion in the kidney. The distribution of the lesion is *partial.* This adjective is used in contradistinction to a *diffuse* distribution of the lesion, such as is typical of chronic parenchymatous nephritis, in which all or most of the glomeruli are affected, and in contradistinction to a *focal* distribution of the lesion, such as is typical of Libman's kidney, in which occasional glomeruli are affected (focal embolic nephritis).

The distribution and shape of the lesion are shown in Fig. 9, Plate 7, as dark wedge-shaped subcapsular areas based on the capsule and pointing towards the cortico-medullary zone. These wedges are mainly areas of fibrosis corresponding to the depressions between the granulations on the surface of the ordinary granular kidney. When these depressions are small and numerous the surface is so finely granular as to be almost smooth; when deep and more widely distributed the kidney is coarsely granular. The granulations themselves consist chiefly of bunches of convoluted tubules; they are often paler than the intervening depressed areas because they contain less blood.

In tangential sections the lesion is completely irregular; in serial tangential section it is most marked under the capsule, with which it is continuous, while it decreases in extent as it is traced through the cortex. In more marked cases it increases in intensity in the cortico-medullary zone. It is owing to its continuity with the capsule that the capsule is adherent to the renal cortex in these kidneys and often tears the cortex in being stripped. Within the area of the lesion and in the capsule new vascular channels are formed; the capsule itself is thickened and the process extends to the perirenal tissues, the best evidence of this spread being adherence of the kidneys to the perirenal tissues when an attempt is made to remove them at post-mortem examination. There is in fact 'capsulitis' and 'perinephritis', conditions in every way comparable to perisplenitis and perihepatitis. The similarity of these conditions suggests a similar aetiology. Further, in the presence of this perinephritis there is probably the cause of the lumbar pain in chronic renal disease.

The shape of the cortical lesion has led Jores, Aschoff, and others to attribute the lesion to an obliterative endarteritis of the interlobular arteries and vasa afferentia. This interpretation is correct in some cases (these cases form a definite subgroup to be considered later), but is not necessarily correct in all. If, for instance, the pathogenic agent which causes this wedge-shaped lesion were to reach the kidney via the afferent lymphatics that pierce the capsule to join the perivascular lymphatics of the cortico-medullary zone, a similar distribution of the lesion would result. The possibilities of this path of kidney infection are suggested by the work of Paladini, Blandini, and Kenneth Walker.

Though the shape and situation of the lesion is similar to the lesion that results from minute infarction, it entirely differs from the lesion that results from vascular infection. This lesion is shown in Fig. 10, Plate 7, which is drawn from a specimen of acute suppurative nephritis occurring in a case of infective endocarditis. The marked difference in the shape and distribution of the lesions in these two conditions is interesting.

Fig. 11 shows a single wedge-shaped subcapsular lesion in detail. It is drawn from Case No. 15, male, aged 36, who died of diabetes mellitus. In this case, in spite of most careful search, I could find no evidence of arteriole obliteration either partial or complete. It is, of course, impossible to absolutely exclude such arteriole lesion, but there was no histological evidence of its presence. The lesion is seen as a wedge-shaped area of fibrosis of the distribution and form

already described; with it there are a massive small-cell infiltration and atrophy of parenchymatous elements within the lesion.

The cases in which this wedge-shaped subcapsular lesion is the main histological feature are divided into two subgroups according to the presence or absence of signs of 'active inflammation' in the wedges. The signs of active inflammation have already been defined. The crucial evidence is endo- or peri-glomerulitis; presumptive evidence is intensity of small-cell infiltration; see Fig. 12, Plate 8.

Group I. True chronic interstitial nephritis. Kidneys characterized by a *partial* glomerulitis, either an endo- or peri-glomerulitis, or both; the glomerular affection is in the neighbourhood of the wedge-shaped subcapsular lesion; there is typically also a massive small-cell infiltration by no means proportional to the degree of glomerular tuft damage.

Group II. True arterio-sclerotic kidneys. Kidneys characterized by *partial* glomerular degeneration, fibrosis, and atrophy without signs of glomerulitis. The distribution of the lesion is the same as in Group I; the kidney tissue, as in Group I, is relatively normal (between the lesions); there is little small-cell infiltration, and what small-cell infiltration occurs bears some relation to glomerular tuft damage. This group may be divided into two subdivisions according to whether the accompanying vascular lesion is of the type of diffuse hyperplastic sclerosis or senile arterio-sclerosis. The cases on which this distinction is based are shortly summarized as follows:

Group I.

Case No.	Sex.	Age.	Heart-weight.	Cause of Death.
10	♂	47	19½	Cerebral haemorrhage
18	♂	76	14½	Cerebral haemorrhage
22	♂	76	19½	Uraemia
61	♂	36	32½	Cerebral haemorrhage
65	♂	52	28	Heart failure
29	♂	46	18½	Heart failure
31	♂	29	12½	Aneurysm abdominal aorta
56	♂	56	15	Uraemia
25	♂	67	24½	Cerebral haemorrhage
26	♂	66	17½	Uraemia

Group II.

8	♂	51	28	Heart failure
13	♂	44	11	Gastric ulcer, haematemesis
14	♀	43	13½	Cerebral haemorrhage
16	♂	57	15	Toxaemia
2	♂	53	19½	Cerebral haemorrhage
27	♂	51	11	Cerebral haemorrhage
34	♂	47	14¾	Cerebral haemorhage
64	♂	83	13	Toxaemia

In other respects than the histological criterion as to the presence or absence of active inflammation there is no absolute criterion by which the two groups may be distinguished. There are, however, some broad differences. Thus the average heart-weight is greater in Group I than in Group II. No cases died of uraemia in Group II, whereas 3 died of uraemia in Group I. Cases Nos. 16 and

64 are in this connexion referred to as dying of toxaemia. The determining cause of death was prostatectomy, and so long as there is doubt as to the actual definition of 'uraemia' it is justifiable to distinguish the fatal ending of these cases from true uraemia by the term toxaemia. It was at any rate only a terminal condition.

All cases in Group I died in some way typically associated with arterio-sclerosis or renal disease, viz. cerebral haemorrhage, uraemia, heart failure, and aneurysm. Cases in Group II, on the other hand, died either in some way typically associated with arterio-sclerosis or of an intercurrent complaint. Except for the cases dying of cerebral haemorrhage they are better regarded as cases in which the vascular-renal lesion is merely found incidentally in post-mortem examination.

The following type cases are described:

Group I. Case No. 10. C. B., aged 47, occupation painter, admitted to St. Bartholomew's Hospital, care of Dr. Tooth, complaining of pain in right side of body and numbness and tingling of both hands. He also complained of vomiting about once a week. H.P.C.: July, 1918, patient fell unconscious at a cricket match and was said to have remained unconscious 11 days. Diagnosis of influenza was made. The symptoms for which he was admitted dated from this attack. P.H.: 20 years ago lead colic. February, 1919, haemoptysis three to four times in a week. P.C.: B.P. 235/170 mm. Hg. W.R. negative. Urine 1,010; albumin 0·1 per cent.

Heart hypertrophied. While in hospital this patient made good progress and was shortly to be discharged when one midday he had a cerebral haemorrhage and died.

Post-mortem, 22.2.19. Cerebral haemorrhage. Chronic interstitial nephritis. Atheroma. Hypertrophied heart. Cerebral haemorrhage, old and recent. *Brain*: Right intracerebral haemorrhage, plough up of basal ganglia ruptured into lateral ventricle. Small recent haemorrhage into pons. *Heart*: 19½ oz. Myocardium firm. Valves and pericardium normal. Much hypertrophy left ventricle. Both coronary arteries showed large plaques of nodular sclerosis without calcification. *Aorta*: Nodular sclerosis marked without calcification. *Kidneys*: Weight together 10½ oz. Both small and dark red in colour, adherent to perirenal tissues. On section, cortex diminished and contained a few small cysts. Vessels in cortico-medullary zone prominent and line of demarcation between cortex and medulla was ill-defined. Peripelvic fat was increased. Capsule stripped with difficulty, tearing cortex, leaving coarsely granular uniform dark red surface.

Histology. Type: true chronic interstitial nephritis. Typical wedge-shaped distribution of lesion characterized by marked fibrosis and massive small-cell infiltration; associated with these areas partial glomerulitis. Glomerular affection was chiefly an endoglomerulitis with adhesion of tuft to capsule; periglomerulitis only shown in increased periglomerular fibrous tissue. Typical diffuse hyperplastic sclerosis in which the main change was seen in a marked intimal thickening of second size arteries. Fatty obliteration of arterioles present, but less prominent. The vascular lesion is drawn in Fig. 1 and is entirely typical of diffuse hyperplastic sclerosis.

The following organs were examined for the state of their intimate vasculature: Diffuse hyperplastic sclerosis was found in the spleen, brain, and liver. The heart, skeletal muscle, and lung were normal. Aorta showed ordinary nodular sclerosis in which underlying media was fatty; in another part true atheroma. Carotid artery showed marked intimal thickening and fatty degeneration; radial artery marked intimal thickening without fatty change.

Summary. Active inflammation is shown in the presence of endoglomerulitis and massive small-cell infiltration; diffuse hyperplastic sclerosis was a prominent feature.

Case No. 61. J. W., aged 36, admitted to St. Bartholomew's Hospital, care of Dr. Tooth, suffering from cerebral haemorrhage. The history of the case was not available.

Post-mortem, 14.10.19. Cerebral haemorrhage. Right basal ganglia ruptured into ventricle; arterio-sclerotic kidneys; cor bovinum. Very large fat man, face deeply cyanosed. *Brain*: Vessels at base normal. Plough up of right basal ganglia. *Heart*: 32½ oz., pericardium embedded in fat. Very marked hypertrophy left ventricle. Myocardium somewhat soft. Valves and pericardium normal. Coronary arteries normal. Aorta normal (except for a few small longitudinal fatty plaques). *Kidneys*: 13½ oz. together. Not adherent, small for size of man. Dark red in colour, a few cysts in each cortex. Capsule stripped easily, leaving smooth evenly-coloured surface. Cut surface uniform in colour; cortex narrow; some increase in size of pelvis; vessels in boundary zone unduly prominent.

Histology. Type: true chronic interstitial nephritis. *Kidneys*: Typical wedge-shaped distribution of lesion in which massive small-cell infiltration was a most prominent feature. It was in part perivascular in the cortico-medullary zone.

This specimen shows typical periglomerulitis, and three glomeruli thus affected, and seen in one two-thirds field in the neighbourhood of one of the patches of interstitial subcapsular inflammation, are drawn in Figs. 13, 14, and 15, Plates 9 and 10. These figures show the massive small-cell infiltration, the relatively normal glomerular tuft in Fig. 13, and the cellular proliferation of the epithelial cells that form the parietal layer of Bowman's capsule resulting in concentric ringing of the tuft, especially marked in Fig. 14. These figures demonstrate the use of the term 'periglomerulitis'. It is emphasized that the process is a cellular proliferation and not simply a fibrosis; it is, in fact, evidence of 'active inflammation' in contradistinction to 'replacement fibrosis'.

Some of the glomeruli show hyaline degeneration as in Fig. 15, others show fatty degeneration in the glomerular tuft. The great majority of glomeruli are normal. The vascular change is a partial hyaline and fatty degeneration of the capillary nexus in some of the affected glomeruli, together with very marked and characteristic diffuse hyperplastic sclerosis.

The intimate vasculature of the following organs was examined: Diffuse hyperplastic sclerosis was found in the spleen, liver, and pancreas. The intimate vasculature of the heart, stomach, large intestine, and lung was normal. Aorta showed fatty degeneration and thickening of the intima. The carotid showed a similar change, less marked. The radial artery was relatively normal.

Summary. This case is further illustration of true chronic interstitial nephritis in which periglomerulitis is evidence of active inflammation and massive small-cell infiltration is confirmatory evidence. It is further evidence that the process underlying diffuse hyperplastic sclerosis is one of active inflammation.

Group II. Case No. 14. E. G., aged 43, admitted 20.3.19, care of Dr. Morley Fletcher; brought in by police unconscious, in a fit. P.C.: Hemiplegia right;

aphasic and half-conscious. P.H.: Complained of headaches lately. H.P.C.: The day before complained of feeling stiff; then fell; complained of pain in left side; recovered almost at once and continued work.

Post-mortem, 24.3.19. Cerebral haemorrhage, chronic interstitial nephritis, granular kidneys. *Brain*: Nodular sclerosis of vessels at base of brain, vertebrals normal. Large haemorrhage into left basal ganglia, plough up, ruptured into ventricles. *Heart*: 13½ oz. Hypertrophy of left ventricle not marked. Valves normal except for slight sclerosis of aortic cusp of mitral. Coronary vessels show nodular sclerosis. Aorta slight atheroma. *Kidneys*: Right 4½ oz.; left 3½ oz.; somewhat tough on section. Right showed little change except for some thickening of smaller vessels which was obvious to naked eye. Capsule stripped fairly easily, leaving a smooth surface. Left kidney was unequally affected. In its upper third, particularly in its outer convex surface, it was considerably shrunken and markedly granular. Its lower two-thirds were relatively normal; the capsule stripped easily, leaving a smooth surface, whereas it was much adherent to the upper pole. On section the cortex was reduced in the region of the fibrosis. The vessels in the cortico-medullary zone were somewhat prominent. In other respects the kidney appeared normal.

Histology. Type of true arterio-sclerotic kidney. Both kidneys showed the same lesion, but it was more marked in the left kidney than in the right. The same wedge-shaped subcapsular fibrosis was present as has been described in kidneys belonging to Group I. There was relatively little small-cell infiltration. In the region of the areas of fibrosis many glomeruli were affected by hyaline degeneration, fibrosis, and atrophy, but there were no glomeruli showing evidence of active inflammation in either an endo- or peri-glomerulitis.

Typical diffuse hyperplastic sclerosis was present and more marked in the left kidney than in the right. The intimate vasculature of the following organs was examined: Diffuse hyperplastic sclerosis was present in the spleen, brain, and liver. There was no arterial change in the heart, skeletal muscle, stomach, small and large intestine, and suprarenal gland. Aorta showed nodular sclerosis. In the carotid there was intimal thickening and fatty degeneration. The intima of the radial was slightly thickened.

Summary. A case of diffuse hyperplastic sclerosis with renal fibrosis, in which, on account of the absence of active inflammatory changes in the renal parenchyma, it is presumed that the vascular lesion is primary, and the renal parenchyma lesion secondary to vascular change. This is, therefore, a case such as is alluded to by Fagge as primary vascular disease. It belongs to the first group of vascular kidneys described by Osler; it is the 'reine Schrumpfniere' of Aschoff; it is Gaskell's 'genuine Schrumpfniere'; it is Adami's 'primary granular kidney'.

Case No. 8. G. S., aged 51, admitted, care of Dr. Drysdale, complaining of dyspnoea and praecordial pain. H.P.C.: Quite well until 1914, when, after a struggle with a man, he complained of dyspnoea. Three weeks later he was quite well and resumed work. January, 1919, dyspnoea returned, followed by vertigo. One week before admission he complained of swelling of legs and cough. P.H.: Bubonocele thirty years ago. Rheumatism six years ago. P.C.: Orthopnoea. Marked aortic regurgitation with cardiac hypertrophy and dilatation. Urine 1,020 ac. 0·04 per cent. albumin. Granular and hyaline casts. B.P., 200 mm. Hg. W.R. +. Died of heart failure, 10.2.19.

Post mortem, 11.2.19. *Brain*: Nodular sclerosis in vessels at base of brain. *Heart*: Hypertrophy and dilatation of left ventricle; syphilitic aortitis. *Kidneys* described as 'arterio-sclerotic'. Cardiac liver and spleen. Infarct of lung.

Histology. Slight wedge-shaped subcapsular fibrosis. Little small-cell infiltration, in fact scarcely any increase. Occasional hyaline degeneration of glomeruli; no glomerulitis. Slight but typical diffuse hyperplastic sclerosis. No evidence of active inflammation. The intimate vasculature of the following organs was examined: Diffuse hyperplastic sclerosis was present in the spleen and brain. The intimate vasculature of the liver, heart muscle, and lung was normal except for a slight degree of intimal thickening in the liver. Aorta showed the microscopic changes of syphilitic mesaortitis. The carotid showed intimal thickening and marked fatty change. The same changes were present in the radial to a less extent.

Summary. There was very little renal lesion, and unless carefully looked for it would have escaped observation. These cases of kidney disease, including both acute and chronic processes of various types, illustrate the concurrence of arterial and epithelial lesions. It has been shown that in the majority of the forms of renal disease described there is histological evidence of active inflammation of the renal parenchyma and at the same time arterial lesions of the type found in arterio-sclerosis. This observation is contributory evidence in favour of the view that arterio-sclerosis is an active inflammatory lesion. In several of the forms of renal disease described it is out of the question that renal disease causes vascular disease or vice versa, yet in comparing the various forms one is gradually led, almost insensibly, to those forms in which the inflammatory factor recedes, and in which the arterial lesion, of problematical inflammatory nature, dominates the picture, the background of the picture being formed by purely degenerative changes in the kidney tissue itself. The view that I have attempted to establish explains this gradual sequence in terms of pathogenic agents of varying kind and intensity, but alike in causing active inflammatory reaction in the tissues they insult, affecting renal epithelium and renal vessels simultaneously in an acute or chronic process. When acute the epithelial reaction dominates the picture, when chronic both epithelial and vascular changes coexist; in the very chronic only the vessels suffer, the pathogenic agent being too feeble to evoke reaction in the epithelial tissues, or these tissues being too feeble to react, they simply atrophy or degenerate. From this point of view a single agent is responsible for vascular and renal disease, and vascular disease is as little the cause of renal disease as the latter is the cause of the former.

D. *Infections as the Cause of Diffuse Hyperplastic Sclerosis.*

This research has thus far led to the general proposition that diffuse hyperplastic sclerosis is an active inflammatory lesion. The common causes of active inflammation are bacterial infections. Several of these have already been discussed as causes of local hyperplastic sclerosis; thus rheumatic fever, tubercle, and syphilis have been found to be the cause of this vascular lesion. There is, however, no evidence that rheumatic fever and tuberculosis are a cause of diffuse hyperplastic sclerosis. Neither disease is clinically recognized as a cause of

premature diffuse sclerosis; neither disease is commonly associated with a raised blood-pressure, and in so far as either is associated with cardiac hypertrophy there is ample cause for this in the cardiac disease of rheumatic fever and the pulmonary disease of tubercle.

These facts of common knowledge are borne out by my analysis of twenty years' St. Bartholomew's Hospital post-mortem records, for I found no case in which the post-mortem record suggested a cardiac hypertrophy due to vascular disease of rheumatic or tuberculous origin. Further, in my series, three cases died of rheumatic fever without post-mortem evidence of diffuse hyperplastic sclerosis. Of these cases, six organs were examined in one, nine organs in another, and three organs in the third.

Evidence, on the other hand, has been adduced of syphilis being a cause of diffuse hyperplastic sclerosis. The statistical evidence suggests syphilis as a cause of death of a certain proportion of cases dying with hypertrophied hearts, these cases having a maximum case mortality about the age of 45. In the second place clinical evidence has established syphilis as a cause of cerebral haemorrhage, especially in those cases that die of cerebral haemorrhage at a relatively early age.

But, though it may be shown that syphilis is a factor in the production of diffuse hyperplastic sclerosis, it cannot be assumed to be the 'actual' cause, as it is of syphilitic mesaortitis; it may be only a predisposing or determining cause. There is no histological difference between the diffuse hyperplastic sclerosis of syphilitic and non-syphilitic cases.

As regards pyogenic agents I cannot bring forward any definite evidence other than negative evidence. Diffuse hyperplastic sclerosis was not found in Case No. 7, male aged 64, and Case No. 60, male aged 38, who died of pneumonia; nor in Case No. 9, male aged 43, who died of influenza; nor was it present in several cases that must have suffered from pyogenic infections of the urinary tract for several years before death. There is one type of vascular lesion which is known to result from chronic infection, namely, amyloid disease, and it is of interest to compare this vascular lesion of known bacterial toxic cause with diffuse hyperplastic sclerosis.

Amyloid disease. My series includes three cases of amyloid disease, Nos. 48, 58, and 71. Nos. 48 and 58 were pure cases of amyloid disease; in Case No. 71 the lesion was combined with diffuse hyperplastic sclerosis of a somewhat atypical form. Amyloid disease results from the circulation of a bacterial toxin in the blood-stream, and, like diffuse hyperplastic sclerosis, the incidence of the lesion on the vascular tree is not uniform; it is not uniform in the length of an artery, nor in the extent of an organ; it also varies in its incidence on the several organs. It differs from diffuse hyperplastic sclerosis in the anatomical distribution of the lesion, as is shown in the following summary of the three cases:

No.	Disease.	Sex.	Age.	Kidney.	Spleen.	Brain.	Liver.	Heart.	Pancreas.
48	Amyloid disease	♂	20	++	++	0	+	±	++
58	,, ,,	♀	13	0	+	—	++	0	0
71	,, ,, assoc. chr. nephritis	♂	26	++	++	+	++	+	—

No.	Disease.	Skeletal Muscle.	Stomach.	Intestine. Large.	Intestine. Small.	Lung.	Thyroid.	Skin.
48	Amyloid disease	0	0	±	+	0	0	0
58	,, ,,	0	0	0	+	0	0	—
71	,, ,, assoc. chr. nephritis	—	—	—	—	0	—	—

No.	Disease.	Ureter.	Lymph. Gland (Pancreatic).	Suprarenal.	Aorta.	Carotid.	Common Iliac.	Dorsalis Pedis.
48	Amyloid disease	—	—	—	0	0	0	0
58	,, ,,	0	++	—	—	0	—	—
71	,, ,, assoc. chr. nephritis	—	—	0	—	—	—	—

— = Not examined.
0 = No amyloid disease.
± = Slight amyloid disease.

In the present series of cases there is no case in which diffuse hyperplastic sclerosis, when present to a marked degree, failed to affect the kidney, whereas in Case No. 58 there was no amyloid change in the kidney though there was marked amyloid change in the liver. Amyloid disease may as often have its chief incidence in the liver or spleen as in the kidney; it commonly affects the gut, though diffuse hyperplastic sclerosis rarely does so. Amyloid disease illustrates the fact that a general circulating toxin known to have a widespread effect on the vascular system in the several organs of the body may in any particular case be as capricious in its incidence as is diffuse hyperplastic sclerosis. In fact as a lesion it shows more vagary, for in one case the liver and spleen may be grossly affected, and in another the kidney may bear the brunt of disease, whereas in diffuse hyperplastic sclerosis it has been shown that, though the incidence of the lesion is partial, it conforms to some sequence in the degree and order in which the several organs are attacked. So far as it goes the comparison of the incidence of amyloid disease with that of diffuse hyperplastic sclerosis leads to the hypothesis that the incidence of the latter lesion is less dependent on the presence of a circulating toxin, but rather dependent on the anatomical features of the arterial distribution and associated with functional or pathological factors concerned in the tissue supplied.

Summary.

1. Diffuse hyperplastic sclerosis is more common in the kidney than any other organ; it is not found in other organs unless present in kidney or spleen; it is always more marked in these organs than in any other organ; it is not found in its typical development in the heart, lung, or skeletal muscle.

2. A new form of acute endarteritis is described. The histological identity of local and diffuse hyperplastic sclerosis is shown; the difficulty of explaining diffuse hyperplastic sclerosis in terms simply of Growth, Involution, or Degeneration is discussed. The conclusion is that the lesion is one of active inflammation.

3. The difference between diffuse hyperplastic sclerosis and senile arterio-sclerosis is one of physiological age response.

4. A causal sequence exists between raised blood-pressure and cardiac hypertrophy. The relation is established between cardiac hypertrophy and diffuse hyperplastic sclerosis. Syphilis and the cause of chronic renal disease are causes of cardiac hypertrophy, and thus, on the evidence brought forward, aetiological factors in the causation of diffuse hyperplastic sclerosis.

5. Cerebral haemorrhage is evidence of arterio-sclerosis, sometimes of diffuse hyperplastic sclerosis; but at present the only adequate clinical evidence of diffuse hyperplastic sclerosis is a persistently raised systolic pressure of 190 mm. Hg.

6. Chronic renal disease is an active inflammatory lesion in most cases, and, since it is closely associated with diffuse hyperplastic sclerosis, this is brought forward as further evidence that the latter is also an active inflammatory lesion. The histological criterion by which true chronic interstitial nephritis may be recognized is stated, and its distinction from chronic diffuse nephritis on the one hand, and from arterio-sclerotic kidneys on the other hand, is defined.

In conclusion, I wish to state that this work, which was interrupted by the war, has been largely done during my tenure of the Lawrence Research Scholarship, and I wish to thank the electors for permission to publish the results. I am greatly indebted to Sir Frederick Andrewes for his advice and detailed criticism throughout; Dr. J. F. Gaskell's histological method is the basis of the work; some of the best material was given me by Dr. B. Spilsbury. I wish to thank Dr. R. G. Canti for his figures of the urea content of the cerebro-spinal fluid in the cases recorded. I would also thank the Visiting Staff of the hospital for their permission to publish the clinical records of their cases.

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DESCRIPTION OF PLATES.

PLATE 3, FIG. 1. The larger of the three arteries is an interlobular artery whose intima is greatly thickened. The lumen is much reduced in size and is filled with red blood corpuscles. The internal elastic lamina is a fine continuous undulating line and forms the outermost layer of the intima resting directly on the media. The intima consists of a hyaline matrix permeated by fine elastic fibrils; these fibrils have a circular arrangement and undulating form; in the intima are a few scattered subendothelial cells. The muscle-fibres of the media appeared normal and showed no evidence of fatty degeneration or fibrosis. The two smaller vessels are vasa afferentia, terminal arterioles; in each the lumen is occluded as the result of swelling of the endothelium; the swollen endothelial cells have undergone fatty degeneration (which is seen in the stippled appearance of the figure) so that under low power the lumen of these arterioles appears blocked by a plug of fat.
Magnification × 230. Case No. 10, pp. 220, 273.

FIG. 2. Section of a hypogastric artery taken from an infant aged 10 months. The internal elastic lamina shows as a thick undulating dark line and its upper part is seen to be split into two layers. The intima within the internal elastic lamina consists chiefly of proliferated endothelial cells which occlude the lumen, the remnant of which is seen in one of the three minute vascular channels in the centre. The subendothelial tissue is much increased and extends beyond the main bulk of the internal elastic lamina up to the media. It is largely made up of hyaline material, especially visible to the lower and right side of the section, and is traversed by numerous fibrils of elastic tissue not seen in the reproduction. The muscle-fibres of the media have a somewhat granular appearance and are indistinctly striated. Numerous new vascular channels penetrate the media and two are seen in the centre of the intima. There is no fatty degeneration.
Magnification × 120. p. 231.

PLATE 4, FIG. 3. Small artery showing acute endarteritis present in liver from a case of icterus gravis. The media is normal and the internal elastic lamina is intact; the latter is seen as a folded band within the media. The lumen is practically occluded by proliferated endothelial cells which have an elongated form and oval nuclei. There is no fatty degeneration or small-cell infiltration.
Magnification × 300. Case No. 46, p. 234.

PLATE 5, FIG. 4. The condition in this artery is similar to that shown in Fig. 3. The lumen is occluded by proliferated endothelial cells, many of which are seen in cross-section. It is possible that some of these are mononuclear cells of the lymphocyte type; this interpretation is, however, rendered improbable owing to the absence of infiltration of the media and the fact that other arteries in the same section show definitely that at any rate the majority of the cells in the lumen are endothelial cells. The massive small-cell infiltration in the tumour was evidence of an acute inflammatory condition.
Magnification × 230. p. 234.

FIG. 5. Cross-section of a meningeal artery showing syphilitic endarteritis. The intima is greatly thickened and consists of hyaline material in which there is a fairly regular fibrillar network. The lumen is much reduced and is lined by endothelium; the inner part of the intima appears to consist of flattened endothelial cells, while the outer part is studded with small round cells which are the result of infiltration from without or in part the result of proliferation of subendothelial intimal cells. The media and internal elastic lamina are intact. The space between the internal elastic lamina and media is an artefact, the specimen being paraffin embedded and xylol cleared.
Magnification × 80. p. 234.

PLATE 6, FIG. 6. Section of a branch of the pulmonary artery taken from a rabbit affected with, but not suffering from, tuberculosis pulmonum (chronic miliary form). The section is stained with Weigert's elastica stain to show the marked proliferation and splitting of the internal elastic lamina. The elastic tissue appears black; other tissues not stained.
Magnification × 60. p. 235.

PLATE 4, FIG. 7. Section of a small artery in the spleen showing a condition typically seen in advanced diffuse hyperplastic sclerosis. No internal elastic lamina is visible. The lumen is almost occluded by a greatly thickened intima, which has undergone marked fatty degeneration and is partly hyaline. The Sudan III stain is diffuse, and in addition has picked out densely stained fat droplets which are seen as dark spots scattered over the intima. The faint outline of the swollen endothelial cells that form much of the intimal swelling is seen, especially to the right, and below on the left. A single red blood corpuscle is seen in the lumen. The media is normal; it is surrounded by cells of the spleen pulp.
Magnification × 300. Case No. 14, p. 237.

PLATE 6, FIG. 8. Section of a glomerulus showing adhesions of the visceral to the parietal layer of Bowman's capsule. The epithelial cells that form these layers of the capsule form a fairly regular covering to the tuft. This covering consists of a single line of cells where the layers are adherent; where the covering is double the visceral and parietal layers are still intact and separated by the intercapsular space. The capillary endothelium of the tuft has largely undergone hyaline degeneration and fatty globules (appearing as indistinct grey spots) are present. The normal arrangement of the capillary loops is lost and most of the cells seen appear to be epithelial cells. The neck of the glomerulus is swollen. Surrounding the glomerulus are dilated convoluted tubules the cells of which are degenerate.
Magnification × 230. Case No. 39, p. 265.

PLATE 7, FIG. 9. Section of kidney drawn to show the wedge-shaped areas of subcapsular fibrosis and small-cell infiltration typical of chronic interstitial nephritis. Apart from these areas, which are shown in black, the rest of the kidney parenchyma was normal. This distribution of the renal lesion is described in the text as 'partial'.
Case No. 18, p. 271.

FIG. 10. Section of kidney taken from a patient who died of ulcerative endocarditis. The black areas are foci of massive small-cell (polymorphonuclear cells) infiltration, the earliest stage of miliary abscesses. It is shown for comparison with Fig. 9, and is an example of the distribution of a lesion in the kidney that results from bacterial blood-borne infection. The glomerular lesion in this case was of the type of focal embolic nephritis, but its distribution was diffuse.
Case No. 72, p. 271.

FIG. 11. Section through a single wedge-shaped area of subcapsular fibrosis such as is characteristically found in chronic interstitial nephritis. The lesion is in an early stage and shows fibrosis, massive small-cell infiltration, and atrophy of renal parenchyma elements in the affected area. Atrophic tubules are visible in the apex of the wedge and in its upper part on the left. There is early hyaline swelling of the capillary nexus of the two glomeruli on the right of the section. The glomerulus on the left is normal. No abnormal vessels were definitely identified in the kidney, though many sections were searched. The depression of the surface at the base of the wedge is natural and not an artefact.
Magnification × 80. Case No. 15, p. 271.

PLATE 8, FIG. 12. A more advanced degree of the same lesion is shown in this section. The tubules show dilatation of their lumens and the secreting cells are somewhat flattened; many showed a diffuse fatty staining with Sudan III. The lesion is only roughly wedge-shaped, and in the affected area there is a great increase of fibrous connective tissue and massive small-cell infiltration. In the upper right corner is a glomerulus showing periglomerulitis and hyaline

degeneration of its tuft; on the left, just above the middle of the section, is a glomerulus similarly affected but in more extreme degree; the uniform and rather oval or spherical grey areas on the right and at the bottom of the fibrotic area are congested capillaries. At the base of the lesion, just above the congested capillaries, is an interlobular artery with intact internal elastic lamina and hyperplastic intima partly occluding the lumen; immediately to its right is a vas afferens cut longitudinally and on the bend, its lumen is blocked by swollen intima which has undergone intense fatty degeneration. This is the only fat-staining tissue in the section, excepting parts of the tubule epithelium.

Magnification × 80. Case No. 18, p. 272.

PLATE 9, FIG. 13. Section of a glomerulus showing an early stage of hyaline degeneration of the tuft, and proliferation of the parietal epithelial layer of Bowman's capsule. In the upper and left environment of the glomerulus there is marked small-cell infiltration.

Magnification × 230. Case No. 61, p. 274.

FIG. 14. The same condition as in Fig. 13 is shown, but in a more intense form. The tuft is surrounded by concentrically arranged proliferated epithelial cells forming the typical picture of periglomerulitis. There is intense small-cell infiltration around.

Magnification × 230. Case No. 61, p. 274.

PLATE 10, FIG. 15. The epithelial layer has not in this case proliferated to any extent; the glomerular tuft has undergone almost complete hyaline degeneration. The small-cell infiltration is intense.

Magnification × 230. Case No. 61, p. 274.

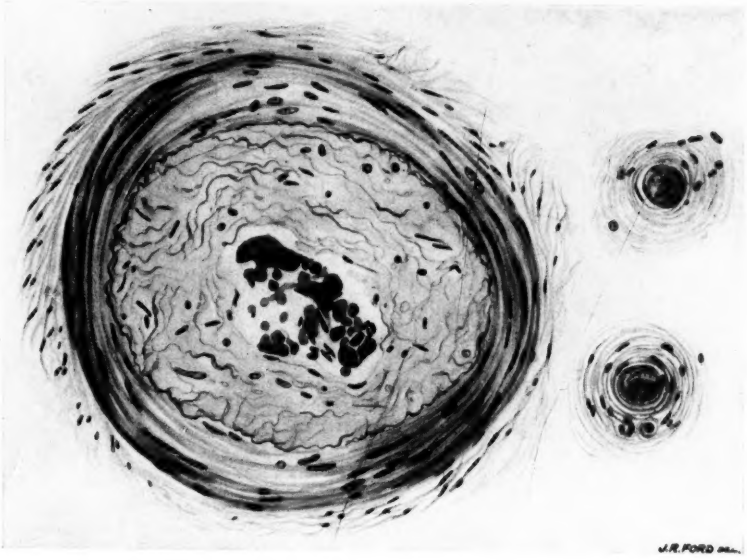


FIG. 1

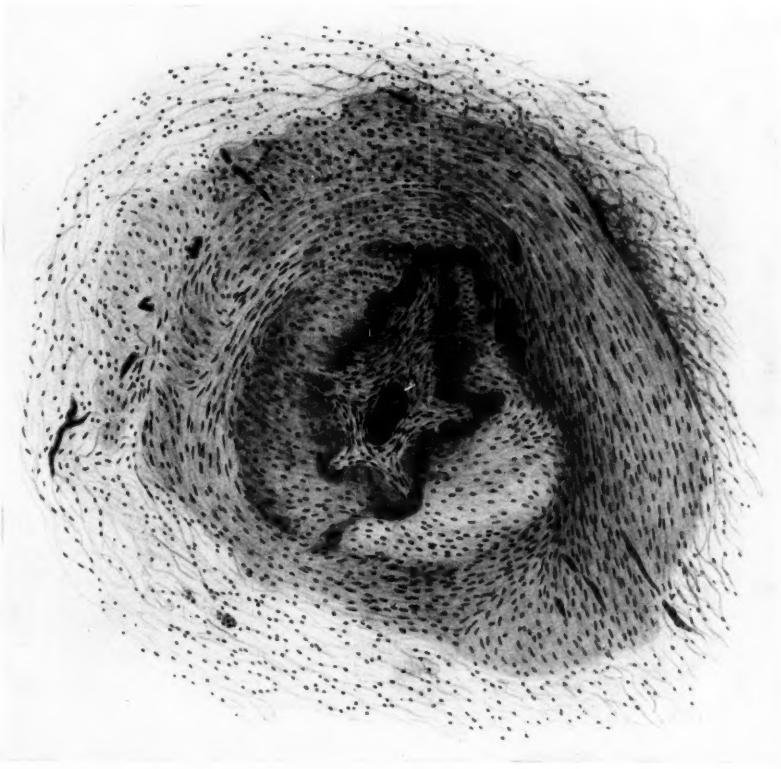


FIG. 2

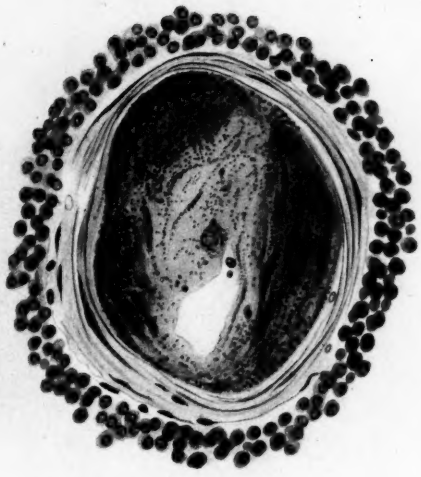


FIG. 7

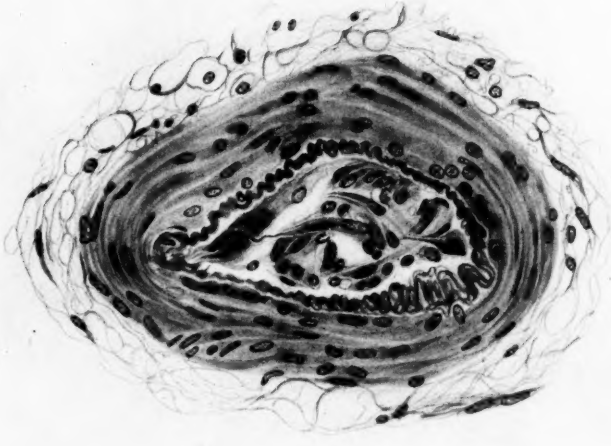


FIG. 3

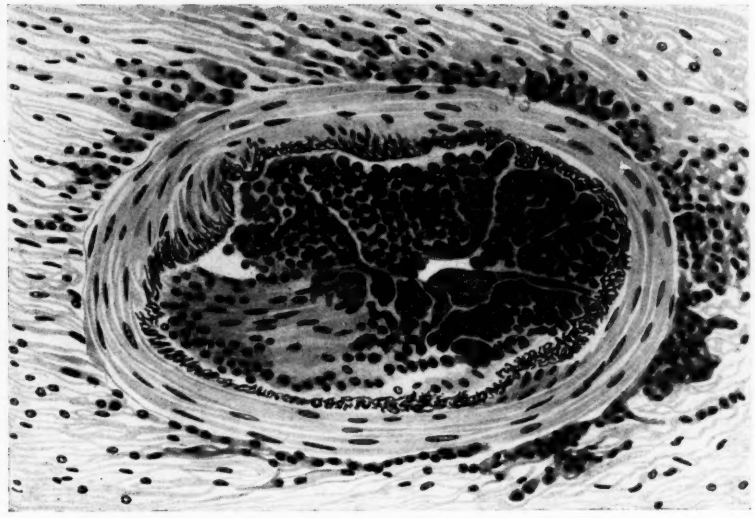


FIG. 4

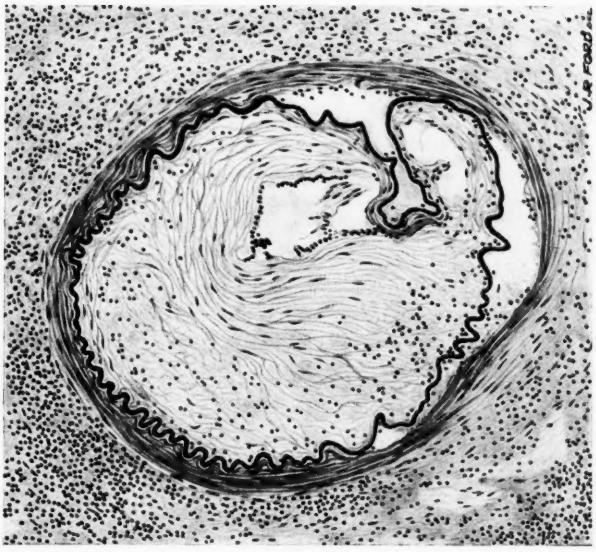


FIG. 5

FIG. 6

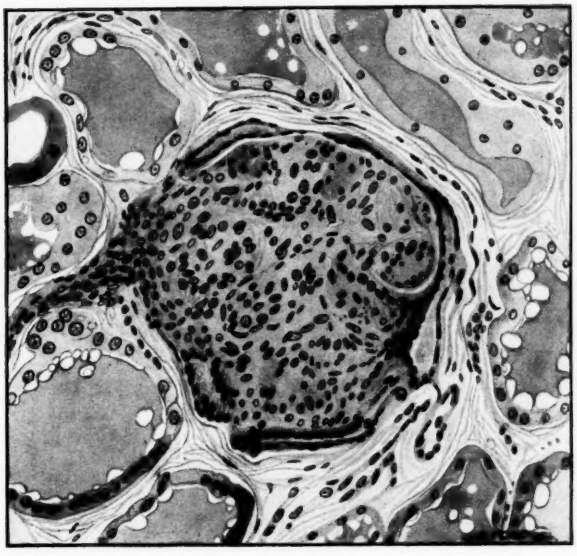
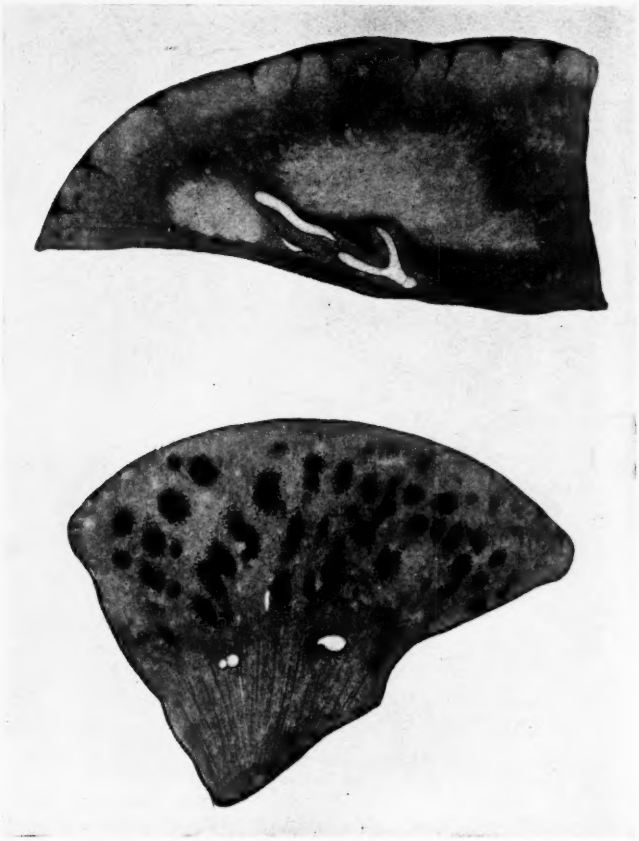


FIG. 8



FIGS. 9-10

FIG. 11

FIG. 12

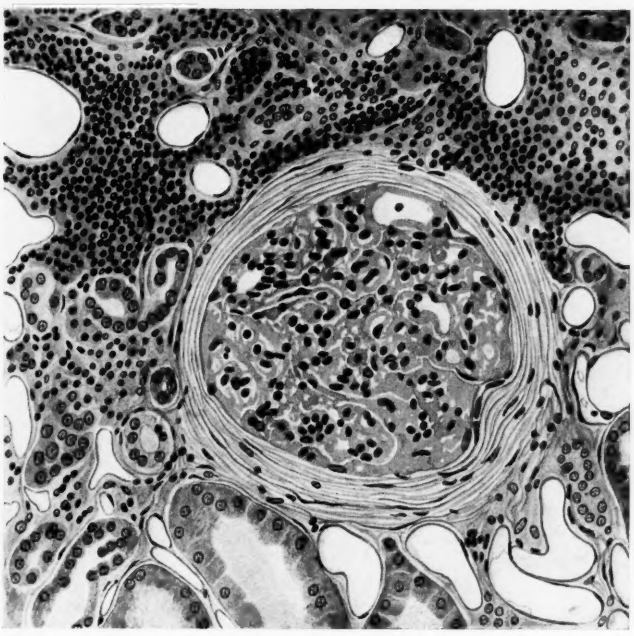


FIG. 13

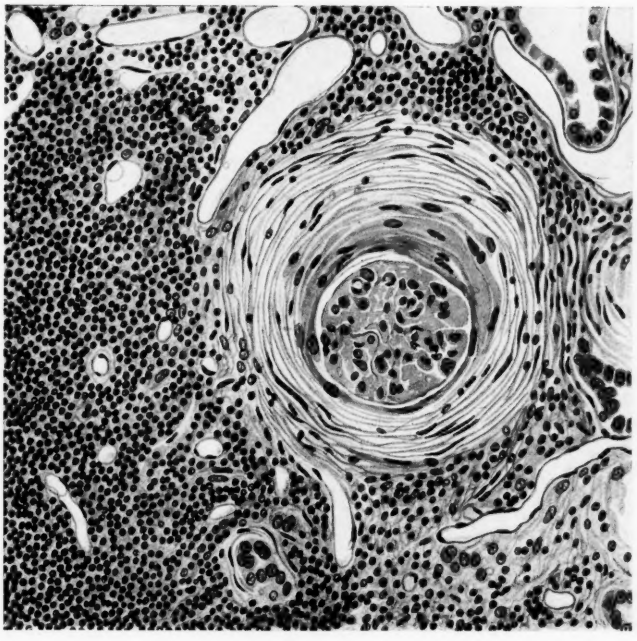


FIG. 14

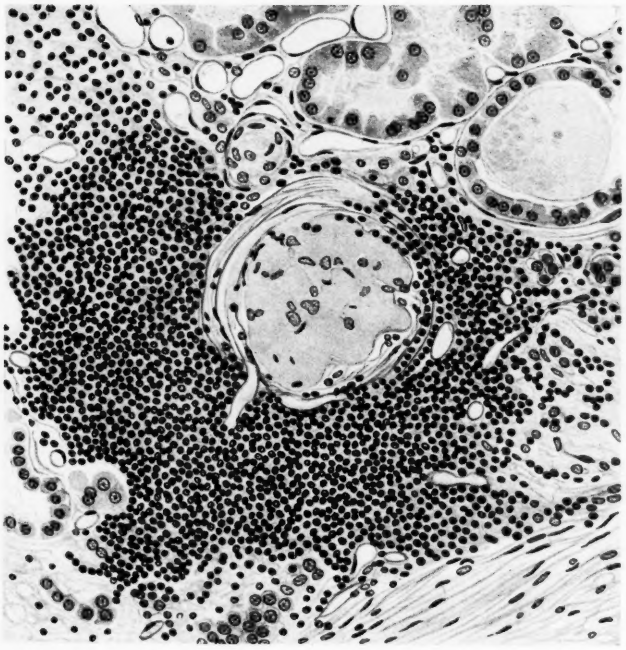


FIG. 15

CRITICAL REVIEW

ENCEPHALITIS LETHARGICA

By C. P. SYMONDS

Historical

In the month of April 1918 there began to appear in various parts of England a disease which presented the signs and symptoms of a toxic or infective process with a selective incidence upon the nervous system. The main features of the earliest reported cases (4, 8) were signs of general intoxication, bilateral ophthalmoplegia, and excessive drowsiness, which symptoms, arising at a time when much tinned food was being consumed in this country, gave rise to the suspicion of Botulism (3, 5). However, the attempt to establish the presence of *Bacillus botulinus* in connexion with the disease proved a complete failure, and, with the occurrence of many other similar cases during the next few weeks, it became evident that we were dealing with an epidemic of unfamiliar type, in which food poisoning played no part in the aetiology.

Occurring as they did almost simultaneously with a widespread epidemic of influenza, which overran all Europe at this time, these cases at first were not unnaturally deemed manifestations of the action upon the nervous system of the influenzal poison, and large numbers of them were doubtless recorded by the medical profession under categories other than that of encephalitis lethargica. The latter title had already been proposed by Economo (10) to describe an epidemic disease which appeared in Vienna in the spring of 1917; and an analysis of his report leaves no doubt in the mind of the reader that his cases belong to the same category as those which made their appearance in England a year later.

In France similar cases had already begun to appear in such numbers as to evoke a paper by Netter (11) at the Société Médicale des Hôpitaux de Paris in March, followed by similar reports from many sources (45, 46, 48). Netter seems to have been the first to identify the new disease with that observed by Economo and to be responsible for the perpetuation of the title—encephalitis lethargica.

Netter also drew attention to the history of a mysterious disease called 'Nona' (13), which, appearing in northern Italy in 1890, assumed epidemic proportions there and cropped up in various parts of Europe during the next two years.

[Q. J. M., April, 1921.]

Summarizing the main features of Nona in a paper written from Paris in 1892, Longuet (2) laid most emphasis upon the lethargy, which was, he says, of a type not met with in any other disease and deserving the appellation 'coma somnolentum'. The condition is thus described in one of the cases quoted by him: '. . . on l'interpelle à très haute voix; il répond quelques mots articulés: il ouvre les yeux, on lui présente quelques objets, qu'il désigne parfaitement, puis fait mine de s'endormir immédiatement; si on lui demande pourquoi il dort, il répond que "ça l'oblige à dormir".' He further mentioned ptosis, inequality of the pupils, stiffness of the neck, deep-seated pains, patchy anaesthesia, and absence of tendon reflexes as occurring in various cases.

He also quoted Mauthner's (1) hypothesis that the disease was of the nature of an acute haemorrhagic polioencephalitis superior, and that the pathological drowsiness was explicable on the basis of inflammatory changes affecting the grey matter in the floor of the third ventricle and aqueduct of Sylvius, where there are presumed to exist centres connected with the regulation of sleep.

From this account it appears that the main features in the symptomatology of Nona closely resembled those of encephalitis lethargica, and it is interesting to notice that both diseases coincided in their appearance with a world-wide epidemic of influenza. Furthermore, at a discussion upon encephalitis lethargica in New York in 1920, McCarthy drew attention to the fact that following the influenza epidemic in the United States in 1889 there occurred in successive years a series of smaller epidemics, each of which was associated with a number of cases of encephalitis closely resembling those seen at present.

In its epidemic form encephalitis seems to have died out completely, but reference to case reports, such as those of Collier (99) and Ramsay Hunt (91), together with other instances personally communicated, has led the writer to the impression that sporadic cases were occurring during the period intervening between the decline of Nona and the origin of the present outbreak. Ramsay Hunt (91), for instance, records three cases of the acute myoclonic type seen at intervals during this latent period, and in a case known to the writer a medical man had in 1911 what would now be regarded as a typical attack of the lethargic and ophthalmoplegic type, with complete recovery.

The question is complicated by the fact that ophthalmoplegia and probably lethargy are signs due to the localization of the virus and not of its specific character, and may therefore occur in cases of encephalitis due to various causes. But it is at least probable that the disease now recognized as encephalitis lethargica represents not the appearance of a new virus but the acquisition of a new virulence by a germ long smouldering. Of the causes leading to such a conflagration we know little, but may consider as analogous the recent outbreaks of cerebrospinal fever in epidemic form after a long period of desultory sporadic incidence.

However, the present epidemic has been generally recognized by the medical profession as a new disease. During the summer of 1918 it assumed proportions in this country warranting an inquiry by the Public Health Department of the

Local Government Board. Towards the end of the year it died down, although sporadic cases were still occurring with some frequency.

There appeared to be a mild recrudescence during the winter months, after which even the sporadic cases became rare until the following November (1919), when a further small epidemic appeared and continued until the early spring. Subsequently very few cases were seen until November, 1920, when a further outbreak appeared, and flourishes at the moment of writing (January, 1921), so that the reviewer has seen three fatal cases at Guy's Hospital during the past ten days.

On the continent of Europe the seasonal incidence has been very much the same. In March, 1919, the first series of cases was reported from the United States of America (50, 51, 52, 53), since when the disease has spread slowly over that continent and is still prevalent, showing the same tendency to die out during the summer and reappear in the winter months, and the same clinical variations as have been observed in Europe.

Mention must also be made of an epidemic of encephalitis which reached serious proportions in Australia during the year 1917, and was carefully studied by Breinl (12), who considered it to be an aberrant form of acute poliomyelitis. Perusal of his report in the light of subsequent observations suggests to the reader that both clinical and pathological evidence exists for supposing that this epidemic may have been rather akin to encephalitis lethargica.

This impression is strengthened by the histological reports of Cleland (28), who subsequently succeeded in transmitting the disease to the monkey, sheep, calf, and horse by intracerebral inoculation of material obtained from the brain and cord in human cases, and preserved in glycerin. In these animals he also found the perivascular cuffing which has come to be considered typical of encephalitis lethargica. Cleland considers that the disease was not identical with acute poliomyelitis. On the other hand, there are points of difference from encephalitis lethargica, of which the most important is that the cases reported by him, as well as those of Breinl, occurred in the late summer and autumn, in hot dry parts of the country. On the clinical side also the ophthalmoplegia typical of encephalitis lethargica does not appear a prominent feature in the Australian epidemic. The evidence is thus rather inconclusive.

Excluding this outbreak, we note that the disease under consideration first appeared in Vienna in the late winter of 1917, subsequently manifesting itself in France and England in 1918 about the same time of year, and in North America again at the same season one year later. Thus the epidemic seems to have spread slowly from east to west, and to have been favoured in its progress by the climatic conditions of the winter season.

Epidemiology.

The new epidemic in this country was the subject of an official report in 1918, containing the results of an inquiry made by S. P. James (56). It was found that the cases reported were from all parts of the country and were roughly

proportional to the head of population in the different areas. It was evident therefore that there was no epidemic centre, but that the disease was widely, if sparsely, disseminated throughout the country. The graph representing the seasonal incidence showed a definite peak in the months of March and April, 1918, which may have been partly due to the awakening of public and professional interest at that time. Since then the general impression has been gained that there has been an annual winter rise in the number of cases, with the highest incidence in the months of January and February. This is corroborated by the chart showing the weekly notifications for the first three months of 1919, issued in the Report of the Local Government Board (55), and by those shown by Bramwell (58) for his fifty-seven cases in the years 1918–20. Reports from the various countries of Europe and the continent of America are agreed upon the fact that the epidemic is thinly disseminated throughout the population.

James (56), making further inquiry into the comparative age incidence, distribution, and mortality of the new disease and acute poliomyelitis, came to the conclusion that no evidence is to be obtained from these points to show that encephalitis lethargica is an aberrant form of poliomyelitis, an opinion since widely supported on clinical and pathological grounds, though at one time stoutly opposed by Crookshank (7).

There is no very solid evidence as yet to show that the disease is infective in the sense that it may be conveyed to one human being by another.

In a few instances (74, 78) two cases have occurred in the same house, but the patients may have acquired the infection from an environment shared in common. Reece and Macnalty in their 1919 report (55) record several such cases.

Of more importance is a record by Macnalty (57) of an outbreak of encephalitis in a girls' home near Derby in August, 1920, where there occurred twelve cases with five deaths. In the fatal cases of this series, although the clinical features resembled those of encephalitis lethargica, pathological examination failed to reveal the characteristic picture. Moreover, the occurrence of gastro-intestinal symptoms in some of the abortive as well as in the more serious cases suggests the possibility of *Bacillus botulinus* as the true causal agent. On the other hand, a monkey inoculated with the nervous tissues of one of these cases developed lethargy and tremors, and examination of the brain after death showed microscopical lesions resembling those of encephalitis lethargica. So far no similar outbreaks have been recorded, and it appears wiser at present to suspend judgement upon the possibility of direct communication of the disease from one person to another.

Pathological Anatomy.

Most observers are agreed that in the majority of cases macroscopic examination of the brain and spinal cord shows very little abnormality beyond congestion of the meningeal and intracerebral capillaries, which may be but little marked in an acutely fatal case.

In rare instances subdural haemorrhages may be present, sometimes of a considerable size, as in the cases in which the condition was discovered at operation by Buzzard and Sargent (90). There may also be haemorrhages in the substance of the brain, especially in the grey matter of the basal ganglia and mid-brain: in a case recorded and figured by Wilson (104) confluent haemorrhages gave rise to a comparatively large extravasation in the region of the locus niger. Similar appearances have been reported in the cerebellum (58) and cerebral hemispheres, and Buzzard (90) has called attention to the possibility of mistaking such a haemorrhage in the region of the internal capsule for that due to the commonplace rupture of a sclerotic vessel.

In a typical case, in addition to the injection of the membranes already mentioned, section of the brain shows the cortex to be of a reddish colour (due to capillary congestion) which varies from a faint flush to a decided salmon pink.

The minute vessels severed in cross-section are all agape and oozing bright blood. In the grey matter of the basal nuclei and mid-brain, and sometimes in the spinal cord, is observed the same pink colour as that seen in the cortex.

Microscopical examination of stained sections after hardening reveals appearances which, as described in similar terms by many different observers, appear characteristic of the disease. Reference to the descriptions given by Wilson (104), Marinesco (17), Pierre Marie (14), Miller (58), Buzzard and Greenfield (59), Wegeforth and Ayer (15), Mott (71), Bassoe and Hassin (19), and Calhoun (18), makes it abundantly clear that the features of most importance are vascular congestion, evidence of toxic degeneration of nerve-cells and neuronophagia, proliferation of the mesoblastic cells of the vessel walls, infiltration of the perivascular (Virchow-Robin) spaces with small round cells, and glial proliferation. As to the presence of microscopic haemorrhages, Wilson (104) gives the impression that they were a striking feature in his cases; subsequent observers, however, comment upon their rarity, and make this a point of differentiation between the histological picture in this disease and that of acute poliomyelitis. It appears probable, therefore, that Wilson's two cases were somewhat atypical, and that haemorrhages should not be considered a constant feature in the histopathology of encephalitis. When they do occur they are mainly of the nature of perivascular oozings, so that, as Marinesco (17) describes it, the vessels appear to float in a pool of blood.

There is some difference of opinion also as to the specific nature of the changes seen in the nerve-cells. Miller (58) argues that these are frequently no more than can be accounted for by post-mortem decay, and quotes McIntosh in his support.

Other observers, however, including those most expert in neuro-pathology, are agreed that degenerative changes in the nerve-cells are constantly present, but are not universal: in one nucleus a few cells may be severely affected while the remainder are intact: the nature of changes is that ordinarily observed in degeneration, swelling and eccentricity of the nucleus, chromatolysis, and neuronophagia.

There is general agreement as to the constancy of perivascular infiltration, but some discrepancies in the interpretation of the picture. From a study of various reports it appears that both the vessel-walls themselves and the perivascular spaces may be infiltrated with cells, the majority of which are lymphocytes, with the presence of some large mononuclear cells laden with pigment granules. Buzzard and Greenfield (59) consider these cells to be of the nature of scavengers returning to the vessels laden with products of degenerated nerve-cells; this theory is entirely opposed to the view held by others already mentioned, that nerve-cell destruction is an unimportant feature of the disease. The authors quoted bring forward in favour of their view the fact that in very early cases there may be vascular congestion with nerve-cell degeneration without any perivascular cuffing.

The fact that in a case of encephalitis lethargica terminating fatally in the early stages histological examination may reveal very little abnormality is emphasized by the observations of Lereboullet and Hutinel (16). These authors record the results of a detailed examination of the nervous tissues in a typical case of the disease, being able to demonstrate only vascular congestion in the mid-brain, without any perivascular cuffing. These observations fall into line with the well-known fact that, as the result of an acute toxic process, the function of cells may be lost before demonstrable structural alterations have occurred.

No organisms have been described in microscopical sections, but Calhoun (18) reports the presence in one case of rounded homogeneous bodies in the cord and posterior nerve roots. These were found not in the nerve-cells but in the interstitial substance. Pierre Marie (14) describes 'inclusions homogènes' in the cells of the red nucleus, and in a recent paper Da Fano (21) has reproduced drawings of minute granular bodies in the nerve-cells, and also in the salivary glands, which, according to Netter and Durand (quoted by Da Fano), show pathological changes in most cases of epidemic encephalitis. Da Fano puts forward the tentative suggestion that these bodies may be due to the presence in the tissues 'of a living agent, cause of the disease', and compares the Negri bodies of rabies. In view, however, of the fact that these granular masses have not been found by other observers in the course of many examinations during the past three years, it seems most likely that they are accidental appearances, possibly due to the affinity of certain fixatives or stains for products of degeneration. This view is borne out by the observations of Meleny (22), who describes similar granular masses in the nerve-cells which he discovered in the course of experiments with new staining methods.

The distribution of the lesions varies greatly from case to case. There is general agreement (48, 53, 104) as to the selective incidence upon the mid-brain and basal ganglia corresponding with the clinical symptoms most commonly recognized. What is perhaps less generally realized is that there is no part of the nervous system or its meninges which may not be affected.

Apart from the cerebral and cerebellar substance and that of the brain stem

and medulla the spinal cord may be widely involved, as in a case seen by the reviewer, in which the most typical changes were observed in the cervical enlargement, and, as shown in the descriptions of Calhoun (18), in which the cord was affected throughout its whole length. This observer also describes inflammatory changes in the spinal meninges.

Of special importance in relation to the symptomatology is the occurrence of lesions of and around the cranial and spinal nerve roots. Hammes and McKinley (65) describe perivascular and diffuse infiltration of round cells in the root of the trigeminal nerve, together with haemorrhage beneath the arachnoid sheath in one of their cases. Loewe and Strauss (37) have observed round-celled infiltration in the posterior root ganglions of the spinal cord, and Flexner and Amoss have noted a like involvement with small haemorrhages and perivascular infiltration. Burrows (75) describes and figures inflammatory changes in most of the cranial nerves.

A further point of importance in the distribution of the lesions is that they are not only widespread but, in the true sense of the word, disseminated. The picture is not that of a focal inflammatory infective process with diffuse spreading, but of multiple patches of infection apparently of simultaneous origin.

Finally, attention must be drawn to the important observations of Economo (85), who has reported the post-mortem findings in a case which ran a chronic course with many remissions, lasting in all two years. In the nervous tissues he found scattered inflammatory foci in every stage, from that of the earliest changes to the healed lesion, showing that the infectious process may remain smouldering for this length of time with recurrent outbreaks at various sites.

Aetiology.

While members of the medical profession in Great Britain were recovering from the first scare of botulism and becoming accustomed to the thought of a new disease, Crookshank (7) published a paper in which he began by suggesting, and ended by definitely asserting, that the disease was not new in any sense of the word, but represented an outbreak of acute infective poliomyelitis (Heine-Medin disease) with predominant involvement of the higher nerve centres.

There appeared at first to be many arguments in support of this view. There had been a widespread epidemic of the Heine-Medin disease in the Eastern States of America in 1916, which Crookshank supposed had since been 'brewing up' in London. Since the papers of Wickman (105), Peabody, Draper, and Dochez (106), and Batten (107), it had been recognized that the grey matter of brain and brain-stem are frequently attacked in the disease. Moreover, the histo-pathological lesions in the nervous system, and the cerebro-spinal findings in the new epidemic, closely resembled those of acute poliomyelitis.

Evidence has, however, subsequently accumulated to show that Crookshank's natural surmise was premature and incorrect. Besides the epidemio-

logical features already quoted, there are many facts to be urged against the identity of the two diseases. The main points of clinical difference are summarized in the accompanying table.

	Heine-Medin Disease.	Encephalitis Lethargica.
Age incidence	Much more common in children	Any age
Onset of general symptoms	Acute and subacute	Usually insidious or subacute
Temperature	At highest before development of paralysis	Often more marked after the development of paralysis
Onset of paralysis	Acute	Insidious
Distribution of lesions	Predominant in spinal cord	Predominant in mid-brain
Course	Brief duration	Long duration: weeks or months
Cerebro-spinal fluid	Increase of lymphocytes fairly constant in early stages: globulin increased	Lymphocytosis inconstant and seldom exceeds 70 per c.mm. Very little increase in globulin
Involuntary movements	Not observed apart from fibrillation	Movements of divers kinds, frequently present at some period

Pathological examination shows further that in encephalitis lethargica microscopic haemorrhages are an inconstant and inconspicuous feature, whereas they are constant and striking in Heine-Medin disease, while the degeneration of nerve-cells and neuronophagia also is more noticeable and more evenly distributed in the histological picture of the latter. Perivascular infiltration, on the other hand, is a more constant feature of encephalitis lethargica.

Thus, there appears to be hardly any positive evidence in favour of the identity of the two diseases; in both there are found the clinical and pathological signs of an acute non-suppurative inflammatory infection of the nervous system, but there is no more reason to infer from this that they are due to the same cause, than there would be for supposing that all cases of infective consolidation of the lungs are caused by one and the same organism.

On the contrary a consideration of the available evidence shows that there are a great many points in favour of the conclusion that the two diseases, encephalitis lethargica and acute poliomyelitis, are of entirely separate aetiology.

Worthy of more serious consideration is the suggestion put forward by Barker (81), Re (72), and others that the new disease may represent an encephalic localization of the virus of influenza. There are several points in favour of such a theory. Without going back farther in the history of influenza than the epidemic of 1890–2, we note the appearance at that time of the diseases known as *Schlafkrankheit* (1) and Nona (13), which from all accounts were uncommonly like encephalitis lethargica. In the present instance, epidemic encephalitis appeared in conjunction with a widespread epidemic of influenza, which had already manifested itself in sporadic outbreaks during the previous two winters. Since that time the seasonal incidence of the two diseases has been very similar, although the number of cases of influenza has become annually very much smaller.

It is true that on the one hand Pfeiffer's bacillus has been found in the cerebro-spinal fluid in certain cases of influenzal meningitis, and that it has not

been reported in the cerebro-spinal fluid or tissues in encephalitis lethargica. On the other hand, the organism in question is by no means universally accepted as the true causal agent in influenza.

The most cogent argument against this theory lies in the differences in the epidemiology of the two diseases, the one being highly contagious and giving rise to local outbreaks in which whole households may be affected at once, the other manifesting a sporadic desultory incidence upon the population at large. Nevertheless, the occurrence of encephalitis in epidemic and pandemic form in association with influenza, both in 1890–2 and now, suggests a definite connexion between the two. The evidence in favour of their identity is at present slight, and it must be admitted that there are other possibilities. An influenzal infection may predispose to infection with the virus of encephalitis lethargica, or environmental factors of a nature unknown may favour the occurrence of both epidemics.

In relation to this point there is clearly no value in clinical observations such as those of Nonne (73), who records under the heading of nervous complications of influenza cases presenting the symptoms of encephalitis. While the causal organism of either disease remains undiscovered their identity also must remain in doubt.

Since the original experiment of Wiesner (38), many workers have attempted the transmission of the disease to animals; Strauss (35, 37) in America, Levaditi (30, 32) in France, Ottolenghi (36) in Italy, and McIntosh (33, 34) in this country have all reported successful results, to which may be added those of Cleland (28) mentioned above in relation to the 'mysterious disease' of Australia. The last-named worker claims to have obtained positive results in the case of five monkeys, employing an emulsion of the brain from a fatal human case introduced by the intracerebral route; he also reports a series of further successes in transmitting the disease from monkeys to sheep and back to monkeys, and from monkeys to a calf and a foal. The number of his successful inoculations totals thirty-five, but as he makes no mention of negative experiments one cannot obtain the percentage of positives.

Summing up the reports of the other workers referred to above, one finds therein only two instances in which clinical and pathological evidence of encephalitis lethargica in a monkey was obtained by inoculation into the latter of an emulsion of nervous substance from a human case. One of these is recorded by Strauss and his co-workers (35), the other by McIntosh (34).

In Strauss's case no evidence is submitted to prove that the case from which the original material was obtained was a true case of encephalitis lethargica, but the work was done at the Mount Sinai Hospital, New York, whence there have emanated excellent clinical studies of the disease, so that one may assume that there was little doubt as to the evidence being complete.

The monkey inoculated became ill on the day after the injection, when lumbar puncture showed 90 lymphocytes per c.mm., and died two days later. Autopsy revealed punctate haemorrhages, perivascular infiltration, and meningitis.

The material, both human and monkey, was cultured aerobically and anaerobically by the usual methods and found to remain sterile.

McIntosh obtained his material from one of the cases observed and reported by Macnalty as occurring in a rather unusual outbreak in a girls' home. Attention has already been drawn (p. 286) to the fact that the diagnosis in these cases may be considered questionable. In this case the patient, aged 17, became suddenly ill after an attack of nose bleeding, and complained of languor, nausea, and stiffness of the throat: she subsequently developed total ophthalmoplegia and died comatose on the eighth day. Neither in this case, nor in another of the same series examined by Turnbull (57), was there any microscopical evidence in favour of the diagnosis of encephalitis lethargica.

The monkey inoculated with glycerinated brain substance had a fit on the sixth day after the injection and died on the fifty-sixth day; during the interval it was 'lethargic, rigid, and trembling'. Microscopical examination of the central nervous system revealed changes typical of encephalitis lethargica.

Against this Levaditi and Harvier (32) and Laidlaw (personal communication) have performed negative experiments.

A single positive result, if proved up to the hilt, is, no doubt, worth more than many negative experiments. On the other hand, the incubation period (24 hours) in Strauss's case seems extremely short, and in McIntosh's case it must be admitted that the original diagnosis of encephalitis lethargica is somewhat doubtful. McIntosh (33) reports successful transmission from his original monkey to another (one positive result against three negatives), and to a rabbit (one out of three injected). The validity of these experiments must, of course, depend on that of the diagnosis in the original human case, and is further impaired by the fact that an uninoculated monkey, kept in the laboratory as a control, developed a disease in every way resembling that of the others, and presented similar microscopical appearances after death.

Loewe and Strauss (39) in a more recent paper present the results of extensive bacteriological investigations. They claim to have grown in pure culture on Noguchi's medium an organism resembling that discovered by Flexner in acute poliomyelitis. This has been obtained in a long series of experiments not only from fragments of brain, but from the nasopharyngeal mucous membrane, nasopharyngeal washings, cerebro-spinal fluid, and blood of infected human beings and animals. The percentage of positive results is high: subcultures carried through several generations have reproduced the disease and its histological picture in animals; and the field covered by control experiments appears adequate. The single point open to criticism is that in one instance only was the organism identified in the tissues or fluids before culture: this was in the cerebro-spinal fluid from a human case of encephalitis. The organism remains virulent after being kept in glycerin for months, and appears to be a filter-passer.

It closely resembles the Flexner body of acute poliomyelitis, but differs from it in the following important points:

1. Rabbits are susceptible to infectious material from epidemic encephalitis and not from poliomyelitis.

2. Monkeys are very susceptible to poliomyelitis and relatively refractory to material from epidemic encephalitis.

3. Spinal fluid from poliomyelitis is innocuous when injected into rabbits and monkeys, whereas spinal fluid from cases of epidemic encephalitis produces lesions typical of the disease.

The authors of this paper refer to somewhat similar results obtained by Bradford, Bashford, and Wilson (29) in 1917, in the case of infective polyneuritis: Loewe and Strauss assume this to have been a manifestation of epidemic encephalitis, as, indeed, appears probable in the light of subsequent clinical studies. It must be remembered, however, that Bradford and Wilson later withdrew their claims in the light of criticism by Arkwright (40).

In connexion with this recent work in America it is interesting to note again Da Fano's (21) discovery of minute globoid bodies in the tissues of fatal cases, and also the claim of Ottolenghi (36) to have produced a fatal disease in guinea-pigs by the application to their nasal mucous membrane of a few drops of the blood or cerebro-spinal fluid from human cases of encephalitis.

The work of Loewe and Strauss (39) appears conclusive, and the identity of their organism as the causal agent of epidemic encephalitis established at least as surely as that of Flexner in epidemic poliomyelitis. Their results have since been fully confirmed by Thalhimer (41).

The Cerebro-spinal Fluid.

In many of the earlier cases reports in the English and French literature the cerebro-spinal fluid was said to show no abnormality. However, in the brief but admirable report of McCaw, Perdrau, and Stebbing (6) published in April, 1918, mention is made of an excess of lymphocytes in three out of six cases examined. Perusal of the literature on the subject since that date shows this to be a fairly good index of the results obtained in large numbers of cases.

It appears that the cell count ranges on the average between 0 and 50 per c.mm. (very rarely reaching 100), that the increase consists entirely of lymphocytes, and that in quite a third of the cases the number of cells is normal (i. e. less than 5 per c.mm.). No careful observations are available from which one might correlate the number of cells with the stage of the disease, but Boveri (26) states that one is more likely to discover an increase in the earlier stages, as in acute poliomyelitis, and Netter (27) has made a statement to the same effect.

On the other hand, it seems probable that the presence or absence of a lymphocytosis depends on the degree and extent of meningeal involvement. The reviewer has no figures of value to present upon this point,

but has formed the impression that this hypothesis is borne out in clinical experience.

It is generally agreed that the globulin content of the cerebro-spinal fluid is very little, if at all increased, and the reducing bodies are not destroyed. It is noteworthy, however, that the colloidal gold curve obtained by means of Lange's reaction occasionally shows definite abnormalities. In certain cases which the reviewer was privileged to see at the Phipps Psychiatric Clinic of the Johns Hopkins Hospital, typical paretic curves were obtained from the fluids of patients admitted on account of mental symptoms during encephalitis lethargica. Davies and Kraus (23) also report cases in which positive curves were found either of the paretic or luetic types.

Symptomatology.

Since the clinical picture in a case of disease affecting the nervous system depends almost entirely upon the distribution of the lesions, it is essential in attempting to understand the symptomatology of encephalitis lethargica to have a clear view of the range of its topographical incidence, together with any selective affinity shown by the virus for particular situations.

Clearly the nomenclature of the disease is at fault: the disease process is by no means confined to the encephalon, nor is lethargy a constant feature in the symptomatology, which, indeed, may be characterized in certain cases by restlessness and over-activity.

On the other hand, there are obvious objections on the score of length and clumsiness to the title given to their paper on this disease by Barker, Cross, and Irwin (81).

The term encephalitis lethargica has clearly come to stay, and must be accepted with the understanding that it is a makeshift title to which a modification of Barker's descriptive definition might well be added under the text-book headings. As Walshe (80) has emphasized in a recent critical review, it is to be expected that such a widespread disease of the nervous system should give rise to a versatile symptomatology in that the structure of this system is so complex, and the functions of its various parts so highly specialized. One may therefore be prepared to encounter innumerable combinations of symptoms in different patients, and in a series of half a dozen cases in which the diagnosis is reasonably certain there may be no factor in the clinical picture which is common to all. These variations in the symptomatology are rendered all the more striking by the fact that, apart from the diversity of the nervous signs, those symptoms which are attributable to general toxic infection are also inconstant in presence and degree.

Walshe (82) in another paper has proposed certain broad classifications for the better grouping of clinical observations, which appear on the whole to be of value. The two main divisions are into general symptoms and nervous symptoms. Under the former heading come the signs of toxi-infection, fever, shivering,

cutaneous eruptions, pains and malaise, gastro-intestinal symptoms such as vomiting, constipation, foul tongue, &c.

The severity of these manifestations of intoxication is extremely variable, and there seems to be no constant parallelism between this and the degree of involvement of the nervous system. Thus, one patient may become profoundly ill with a high fever, and die in the course of a few days without developing any nervous symptoms other than partial ophthalmoplegia and a little muscular twitching, while another may develop a severe degree of involvement of nervous centres in brain or cord without any history of pyrexia or malaise.

Of the nervous symptoms the lethargy and ophthalmoplegia, which when first described in this country gave rise to the suspicion of botulism, tended on account of their striking character to attract perhaps more than a fair share of attention. They are probably a prominent feature in from 60 to 70 per cent. of the cases, although in the present state of our knowledge of the disease such statements are hazardous, for it is probable that, even as it has widened already, our conception of encephalitis lethargica may enlarge still more so as to include many symptom groups not yet generally accepted under this heading.

Of considerable interest in this respect are the cases of acute infective polyneuritis so called, described by Holmes (108), and again by Bradford (29), which occurred in considerable numbers among the troops in France during the war, especially during 1917, the year preceding the development of the epidemic of cases with lethargy and ophthalmoplegia. There are many points in favour of the assumption made by Strauss (39), that Holmes and Bradford were dealing with a preliminary manifestation of encephalitis lethargica. In the latter disease signs of polyneuritis not infrequently occur, and may dominate the picture, as in cases described by Symonds (83) and Macnalty (109). It is true that in acute infective polyneuritis no abnormality was reported in the cerebro-spinal fluid, but the number of instances in which it was examined (Holmes (3), Bradford (4)) is insufficient for purposes of excluding these cases from the larger group. It may be argued that there were no signs in Holmes's and Bradford's cases of the mid-brain localization of the virus which later was so common in encephalitis lethargica, but against this may be raised the observation that the latter disease appears to have run through many clinical variations since its first appearance, and there are analogies in the case of other diseases for such a tendency on the part of a virus to show changes in its selective affinity. It is probable that while the attention of the medical profession was focused on the mid-brain syndrome as the characteristic point in evidence of encephalitis lethargica many cases with other and less striking manifestations of nervous origin, which would now be at once recognized, then escaped diagnosis. It is therefore safe to say that lethargy and ophthalmoplegia are probably less constant symptoms in encephalitis lethargica than is commonly supposed.

There has arisen a tendency, justly deprecated by Walshe (80, 82), to divide cases of the disease into 'types' according to the symptom complex: the futility of such attempts is quickly realized when one comes across a case in which,

during the course of a few weeks, now lethargy, now delirium, now cranial nerve-palsies, now involuntary movements successively dominate the picture. Moreover the classification of cases in pigeon-holes according to the predominant symptom is likely to result in a false perspective, and may lead to failure to recognize widespread involvement of the nervous system as revealed by manifestations of less striking importance. Thus there have been described, in addition to the lethargic group, neuralgic, choreiform, psychic, myoclonic, meningitic, and polyneuritic types among others, but careful examination and inquiry in almost any case will demonstrate that the infective process is hardly ever so strictly localized as these titles would imply. As an instance may be quoted a case which would certainly have been included under the lethargic-ophthalmoplegic heading:

W. G., aged 51, a sewage pumper, was admitted to Guy's Hospital under Dr. Fawcett on January 8, 1921. On admission he had a temperature of 99·8° F., and was pathologically drowsy: he lay quite still with his eyes closed, and could be aroused with difficulty: once awake he would answer questions in a rational manner, but with an abnormally long pause before each response. There was a moderate degree of ptosis on both sides, the pupils were unequal and inactive either to light or on accommodation, and the face was expressionless and mask-like. Some weakness of the left side of the palate was noticed. None of the tendon jerks could be obtained; the superficial reflexes were normal. There appeared to be no sensory loss, but he complained of headache and buzzing in his ears.

At this time, therefore, the dominant picture was that referable to an upper mid-brain lesion: in addition, however, there were the subjective disturbance of hearing (possibly an irritative root lesion) and the loss of tendon-jerks which is probably to be considered as a minimal expression of the affection of peripheral nerves.

On inquiry into the history it appeared that his first symptom was drowsiness coming on gradually on January 1; on the following day he had severe occipital headache with pain and stiffness in the back of the neck: this passed off in the course of 24 hours, and he went to work on January 3 until the evening, when on attempting to add up some accounts he found himself unable to read (paralysis of accommodation): an hour or two later he began to 'see double'. That night he was much bothered by twitching movements which began in the legs, spread to the muscles of the back and arms, and were powerful enough to move the limbs.

These movements gradually passed off and had ceased by the time he was admitted into Guy's on January 8. On January 10 he began to complain of 'rheumatic' pain in his left shoulder and left foot. This again passed off, and on January 18 his condition was much the same as on January 8, except that the pupils now reacted to light (remaining inactive in accommodation) and there had developed irregular symmetrical blinking movements of the eyelids, proceeding continuously about the rate of two per second.

The cerebro-spinal fluid examined on January 8 contained 25 lymphocytes and 0·03 per cent. protein.

In this patient, therefore, a comparatively mild case, there were at various times in the course of his illness signs of basal meningitis, involvement of the oculomotor nuclei, irritation of nerve roots, motor and sensory, and possibly of peripheral neuritis (absence of tendon-jerks).

The above case also illustrates the fleeting nature of many of the symptoms, and the manner in which they are apt to develop one by one with little remissions, as it were the occasional bursting into flame of a smouldering fire. Economo (44, 86), Abrahamson (84), the writer (83), and others have called attention to this feature in some of their cases, and to the chronic course which this smouldering process of infection may run.

The mental picture in this disease has been so far dominated by the prevailing symptom of lethargy as to have attracted less study than it deserves. Abrahamson (77) has attempted an analysis of the mental status underlying the lethargy, and has drawn attention to the frequency with which it is followed by distressing insomnia and depression. Scattered about the literature are many records of cases (64, 67) with abnormal mental symptoms of which the main features have been summarized by Jones and Raphael (98). The writer of the present review while resident in a psychiatric institute in America had some opportunity of observing cases admitted on account of their mental condition, in which the diagnosis of encephalitis lethargica was subsequently made on good clinical grounds. There is no doubt that the disease may begin acutely with excitement and delirium. This may entirely dominate the picture in the initial stages, and then be followed by lethargy as in Walshe's case No. 3 (82), or it may continue throughout the illness, terminating in death (96) or recovery. The delirium is of the nature commonly met with in the toxic psychoses often with occupational reference, hallucinations, illusions, and transitory delusions. Its content may, however, reflect the previous emotional state of the patient, as in one case seen by the writer in which a fireman appeared to be in the greatest distress on account of a breach of duty for which he imagined he was being tried in a court of law.

In milder cases the state of mental excitement may be confined to restlessness, insomnia, and irritability, which is commonly followed by apathy and dullness. This type of mental picture appears to be most frequently associated with movements of the myoclonic form, as pointed out by Ramsay Hunt (91), Ellis (96), Sicard (95), P. Marie (49), and others.

As one might expect in an infective process with a tendency to widespread dissemination, other mental changes characteristic of organic brain disease are apt to occur. Of these Wilson (104) has called attention to the presence of *Witzelsucht* in one of his cases, and the writer has seen the picture of general paralysis of the insane closely simulated. Walshe (82), Abrahamson (77), and others record the occurrence of changes resembling those of Korsakoff's psychosis.

Other cases (98) have been observed in which dementia praecox and melancholia have followed the attack, but these should probably be regarded as instances in which the infection has been merely a precipitating factor in persons already predisposed to the diseases.

Next to the lethargy and ophthalmoplegia, most interest has been aroused by the various types of involuntary movements met with during the illness or in the form of sequelae. Phenomena of this nature are recorded in the earliest case reports, but have since either become more frequent or attracted more attention. The most complete account of them is to be found in the paper by Marie and Lévy (88), which contains a wealth of detailed observations upon the symptomatology of the disease in general.

They lay special stress upon the occurrence of involuntary movements after a latent period following the illness (*syndrome excito-moteur tardif*). This point also was noted by Buzzard (89), and is one of the most remarkable phenomena encountered in connexion with the epidemic. Marie and Lévy (88), collecting these latent cases, found that they were easily divided into three chronological groups, each of which was separated by a few months from a preceding wave of encephalitis lethargica: the interval between the original onset and the development of involuntary movements was as a rule two to three months, more rarely five to six. In a certain number of the cases the initial attack had been recognized as encephalitis lethargica, or was subsequently recognizable as such from a history of ocular palsies and drowsiness.

In a fair proportion, however, the story was that of a mild 'influenza' with apparent recovery in a week or two, the patient resuming his ordinary occupation without symptoms of illness until the development of the motor phenomena; and there were yet other cases in which no history whatever could be obtained of any preceding attack of fever or malaise. These facts, which are confirmed by the observations of others both in this country and abroad, raise a point of considerable interest and importance. It is clear that if we accept the sudden appearance of involuntary motor symptoms in an otherwise healthy individual as evidence of a preceding attack of encephalitis lethargica, we must admit the existence of an abortive form of the disease, the symptoms of which may amount to no more than a mild attack of fever and malaise, or may even pass unnoticed by the patient himself. If this be so and the disease be a specific entity its frequency must be far greater than has been popularly supposed. The recognition of such mild cases may perhaps be considered of slight clinical value, but would obviously be important if in the future it should be proved that the disease is directly communicable, a possibility suggested by the recent experimental work of Loewe and Strauss (39).

In the light of these considerations a study of the minor symptomatology in straightforward cases of encephalitis lethargica becomes a matter of more than academic interest.

Marie and Lévy are convinced, as the result of their clinical observations, of the occurrence of these *formes frustes*, and claim to have been able in many cases

to recognize such an episode in the history of patients who presented themselves for involuntary movements as the first noticeable sign of their illness.

Among the minor symptoms of diagnostic value they set in order of decreasing importance the following:

1. Occipital headache and neck stiffness at the onset. This has been a point of common observation noted by Hall (4).

2. Trismus or difficulty in opening and closing the jaws, with which may be associated pain in the distribution of the lower branches of the fifth nerve.

3. Facial spasms.

4. An abnormally abundant flow of saliva. (Other observers also have recorded the occurrence of true sialorrhoea apart from the drooling in cases of the Parkinsonian type; and the writer has seen two remarkable cases in children in which the condition persisted for months and led to a constant habit of spitting.)

5. Minor degrees of dysarthria (instances of which are also referred to by Macnalty (109)).

6. Fibrillation of the lingual musculature.

7. Sensations of tightness in the throat.

8. Pathological yawning, especially in cases of the Parkinsonian type.

9. Hiccough. (This symptom, previously reported as of frequent occurrence in association with myoclonic contractions, has lately aroused further interest on account of the appearance in France (79, 92, 93) and in this country of abortive epidemics of illness in which persistent hiccough is the chief symptom. Walshe (94) agrees with the French clinicians in believing these cases to belong to the encephalitis lethargica group.)

10. Sensations of respiratory distress, choking, and stifling.

11. Attacks of pain and swelling in the joints, often preceding motor phenomena in the same locality. These are apt to occur somewhat late in the course of the disease.

12. Sensory symptoms of various kinds, including those met with in peripheral neuritis, lancinating pains associated with myoclonic contractions, areas of cutaneous hyperaesthesia, and pains in the muscles and tendons, especially those affected with rigidity or involuntary movements.

Of the various types of involuntary movements recorded the first to attract attention was the choreiform group. These movements, as noted by Marie and Lévy (88), differ as a rule from those of ordinary chorea in being less irregular and more rhythmic. The same observers have coined the term 'oscillations brady-cénitiques' to denote a form of rhythmic tremor which is unlike that met with in any other disease, and is described by them in the following words: 'Elles (les oscillations) représentent des mouvements lents, réguliers, rythmiques, de grande amplitude, prédominants à la racine d'un membre, parfois synchrones pour les deux membres d'un même côté.' These, as Buzzard (89) observes, must frequently appear as sequelae after a latent period.

Tremors of the Parkinsonian type, always associated with rigidity, are of relatively common occurrence and need no comment.

The so-called myoclonic form of encephalitis lethargica began to excite a great deal of interest in France early in 1920. The papers of Sicard and Kudelski (95), Ramsay Hunt (91), Ellis (96), and Economo (87), portray vividly the symptoms and course of this form of the disease. As described by Sicard and Kudelski, an onset of lancinating neuralgic pains with mild fever is succeeded by the appearance of short, rapid, explosive, rhythmical, muscular contractions, which may affect the limbs, face, or diaphragm, a single segment of the body, or the whole musculature. It is not a matter of spasm, contraction, chorea, or athetosis, but of true myoclonic contractions, which may involve a single muscle, or groups of muscles, and are not accompanied by fibrillation.

In addition to the movements covered by this description fibrillary and fascicular twitchings are commonly seen, and Walshe (82) is inclined to regard this whole group of involuntary contractions as an expression of irritation of the motor nerve roots. In support of this view he quotes a case recorded by Sicard and Kudelski (97) in which clonic movements of the upper limbs were followed by weakness of the extensors and wrist-drop—a paresis of peripheral type. He also notes the random distribution of the movements and their frequent association with pains of peripheral or nerve-root distribution. If this theory of their origin be correct it should be supported by histological examination of the nerve roots and their meninges in fatal cases of the myoclonic type, but evidence of this nature has not yet been put forward.

Marie and Lévy (88) have drawn attention to a group of cases in which the musculature of the face, tongue, jaws, and pharynx is especially affected by the occurrence either of involuntary movements or hypertonus. In these patients there may be clonic contractions of muscles or parts of muscles, or rhythmic tremors of antagonistic groups, which in the case of the jaw muscles may result in chattering of the teeth. In certain cases trismus has been observed.

In relation to this group a case recorded by Collier (99) is of interest, as supporting the contention that sporadic cases of encephalitis lethargica were to be met with before the onset of the present epidemic. The patient, a child of six, developed in 1914 symptoms of meningitis with transient squint, and lay in a stuporous condition for three weeks. After her recovery from this condition there remained permanent loss of voluntary power over the muscles of the face, jaw, tongue, and larynx, together with trismus and contracture of the facial musculature. (Cf. also Sainton (47).)

Pathological findings have already been referred to which show that the inflammatory process may extend to the spinal cord, and of this clinical evidence is also forthcoming. At a recent meeting of the Neurological Section of the Royal Society of Medicine, Collier showed a woman in whom, together with the characteristic lethargy and ophthalmoplegia, there existed the classical signs of a lower motor neuron lesion of the leg, paralysis, wasting, and loss of tendon reflexes. Cases in which involvement of the cord is so extensive are no doubt

rare, but most observers are in agreement upon the frequent absence of the tendon-jerks, to which Guillain (100) has drawn especial attention, considering it as evidence of depressed function of the anterior horn-cells. This explanation may hold good for certain cases, but an alternative hypothesis is that the break in the reflex arc is caused by affection of the peripheral nerves; this is supported by the fact that the abolition of tendon reflexes is commonly symmetrical and often complete in all four limbs, and by the existence in some cases of sensory phenomena referable to a polyneuritis.

A full review of the focal symptomatology of this disease is beyond the scope of the present paper. Many different clinical syndromes have been described in relation to lesions of the cerebral hemispheres, cerebellum, basal ganglia, and brain stem. Special mention may be made, however, of the instance in which Buzzard (90) shows how a case of encephalitis lethargica with hemiplegic onset may even at post-mortem be mistaken for a cerebral haemorrhage.

Boveri (101) has called attention to the very common occurrence of paralysis of accommodation, apart from more extensive ophthalmoplegia, and to the fact that the pupils frequently remain active to light while failing to contract on accommodation—a condition the reverse of that described by Argyll-Robertson in tabes.

Both Wilson (104) and Foster Kennedy (53) refer to eccentricity of the pupils as being present in certain of their cases. Reference to this point is omitted in most clinical accounts of the disease, and it is quite possible that ectopia pupillae, which Wilson (103) has shown to be a sign of localizing value in other lesions of the mid-brain, may have been often overlooked.

Optic neuritis would seem to be of rare occurrence. Buzzard (90) has reported one case of the disease in which it was present together with signs of increased intracranial pressure, which proved to be due to a subdural haemorrhage. Melland (102) describes it as present in two cases. The writer (83) records four others in which optic neuritis was associated with the signs of a widespread affection of the nervous system, with changes in the spinal fluid suggestive of encephalitis lethargica. Dunn and Heagey (69) refer briefly to the existence of papilloedema in two out of fifteen cases carefully recorded by them. The point is obviously an important one and may arise in the differential diagnosis between encephalitis and brain tumour.

Nystagmus has been frequently described, and there may be very fine spontaneous nystagmus at rest.

In his early account of the disease Hall (4) laid stress on the frequency of meningeal symptoms, a point which has since been abundantly illustrated in the literature. These appear, however, to be confined in the majority of cases to a slight or moderate degree of neck stiffness and sub-occipital headache, Kernig's sign being very rarely present.

Bramwell (58) in a careful review of his personal observations of the symptomatology gives an excellent account of the mode of onset of the disease, which he points out is as a rule insidious, so that 'even in very severe cases it

may be a few days or even a week or two before the symptoms become pronounced'. In relation to the manner of onset he recognizes four groups of cases: (1) an asthenic or somnolent type, to which the great majority of the cases belong; (2) a meningitic type; (3) an apoplectiform type; (4) a neuralgic type.

The same author considers that febrile disturbance is met with almost as a rule in the initial stages; 'although as a rule slight in degree and frequently apt to escape detection this symptom is important in relation to diagnosis.' This statement is very probably true, though it is repudiated by other observers, e. g. Dunn and Heagey (69), who report pyrexia in only 43 out of 100 cases; the explanation being that the symptoms in the early stages are so slight that the temperature is not taken, and it has sometimes fallen to normal by the time the patient comes under medical observation.

In an analysis of this point in 132 cases in which records of temperature were available Macnalty (109) found evidence of pyrexia in 124; and the remaining 8 all came under observation at a late stage of their illness. In these cases the average maximum temperature was about 101° F., with extremes of 99° and 105°.

Course.

The course of the illness is extremely variable. The mortality in the series of 168 cases reported by Macnalty (109) in 1918 was 22 per cent.; in the cases notified in England and Wales during 1919 (70) it was 50 per cent.; in Bramwell's series (58) of 57 cases personally observed it was approximately 16 per cent.; in the 100 cases in the American literature analysed by Dunn and Heagey (69) 31 per cent.

Of these figures, that obtained from notification returns is certainly too high, owing to the non-inclusion of the milder cases: those given by Bramwell and Macnalty being the result of personal observations are probably nearer the mark, although if the existence of *formes frustes* of the disease be admitted, the conclusion must follow that the mortality figure of 20 per cent. thus arrived at is too high.

As regards prognosis, all observers are agreed that a high temperature is of ill omen; and Bramwell states that 'if the patient survives the first three weeks of the illness the probabilities are all in favour of recovery'. This is borne out also by Macnalty's figures, but it must be understood to refer only to the risk of death.

No statistics are as yet available which show the percentage of cases in which complete recovery takes place. In Macnalty's (109) series of 93 non-fatal cases (which included an abortive group) 23 had recovered by the end of one month, but in 33 recovery was incomplete at the end of three months. In a recent communication from the Ministry of Health, Parsons (70), presumably referring to the same series of cases, states that in many instances the later

stages of the disease have been much prolonged, and that residual symptoms are common. Bramwell, however, believes that, while improvement is always slow, in those cases which eventually recover complete recovery is the rule, though there may be residues especially in the form of apathy and intellectual dullness.

Evidence has accumulated in favour of the belief that after apparent recovery from the initial illness has set in there may develop fresh symptoms of involvement of the nervous system, and that relapses of this kind are not due to cicatricial changes, but to the smouldering activity of the infective virus which occasionally lights up into flame. The case of Economo (85) has already been quoted which he followed for two years through a series of relapses, and in which eventually he found *post mortem*, besides old lesions in the parts originally infected, evidence of recent inflammatory changes in the medulla corresponding with the terminal symptoms of dysphagia.

Harvier and Levaditi (42) have brought forward an even more important point in evidence of the fact that the virus may persist for long periods in an active state. In their case the illness gradually progressed for six months; rabbits inoculated with emulsions of the mid-brain of this patient died, and their brains showed histological appearances characteristic of encephalitis lethargica.

Thus, although the mortality rate after the third week is low, the prognosis as to ultimate duration and complete recovery remains uncertain, at any rate for several months, and in this connexion it is important to recognize the possibility of a latent period of apparently perfect health between the initial attack and the development of involuntary movements. As to the duration and prognosis in this particular group of symptoms the views of Marie and Lévy (88) may be summarized as follows: Generalized choreiform movements of the ordinary type disappear as a rule at the end of a few months; rhythmic localized movements of a choreic type may persist for a year or more and be accompanied by a certain amount of weakness; the bradykinetic movements last on an average for about six months. The tremors which form part of the Parkinsonian picture may persist indefinitely together with the rigidity.

Diagnosis.

In the absence for the time being of any laboratory test of specific value, the diagnosis of encephalitis lethargica must be made on clinical grounds, and is frequently a matter of some difficulty, depending upon the exclusion of other possibilities. It is true that the common type of case with profound lethargy and ophthalmoplegia is comparatively easy of recognition, but even here there are pitfalls for the unwary, as shown in a case described by Bassoe (68) in which a tumour of the third ventricle was discovered *post mortem* though no diagnosis other than that of encephalitis was entertained during life, and in an instance seen by the writer in which the true diagnosis of myasthenia gravis was for some time obscured owing to a similar mistake. Here, as in the case of many other affections of the nervous system, the history of the onset is often of more

value than examination of the patient in enabling the observer to come to a decision.

There exists no doubt the danger, common to all epidemics, of including under the diagnosis 'encephalitis lethargica' cases due to other causes. Many of these may be sifted out by means of the identification of organisms in the cerebro-spinal fluid, or, in the case of syphilitic affections, by the complement fixation tests; nor does there appear to be any excuse for the inclusion under this heading of such a case as that reported by Hala and Smith (62), in which the spinal fluid contained 480 cells per c.mm., of which 84 per cent. were polymorpho-nuclears, and a purulent meningitis was found *post mortem*. In the absence, however, of any absolute criterion of the disease, we are forced to admit the existence of certain cases in which the diagnosis must remain doubtful, and can only hope that the recent cultural studies in America may lead to the development of some laboratory test of practical value. Until this has been achieved the most fruitful source of greater accuracy in diagnosis would seem to lie in a careful study of the finer points in the symptomatology of undoubted cases.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

THIRTEENTH ANNUAL GENERAL MEETING

THE THIRTEENTH ANNUAL GENERAL MEETING was held on Friday, May 21, 1920, at the University Buildings, Manchester.

The President, Sir Norman Moore, was unable to be present, and in his absence the Treasurer, Sir William Hale White, took the chair.

The Minutes of the last General Meeting, having been published in this Journal, were taken as read and confirmed.

The following were elected as President, Officers, and Committee for the ensuing year:

President: Dr. Judson Bury.

Treasurer: Sir William Hale White.

Secretary: Dr. H. Morley Fletcher.

Members for England:—

Dr. J. R. Charles.
Dr. T. R. Elliott.
Professor Arthur J. Hall.
Dr. John Hay.
Professor James Russell.
Dr. William Pasteur.

Members for Scotland:—

Dr. Francis Boyd.
Professor Ashley Mackintosh.
Professor R. Stockman.

Members for Ireland:—

Dr. J. E. MacIlwaine.
Dr. Gilman Moorhead.
Dr. George Peacocke.

The President, Dr. Judson Bury, on his election took the chair.

The following were elected as Honorary Members:

Sir Thomas Barlow, K.C.V.O.
Professor T. R. Glynn.
Sir Wilmot Herringham, K.C.M.G.
Dr. G. S. Middleton.
Sir Norman Moore, Bt.

The following were elected Members of the Association:

George Allison ALLAN, M.B., 22 Sandyford Place, Glasgow. Senior Assist. to the Regius Prof. of Med., Glasgow.

Hugh T. Ashby, M.D., 13 St. John Street, Manchester. Physician Manchester Children's and Salford Royal Hospitals.

Arthur W. M. Ellis, M.D., Dept. of Clin. and Exper. Med., Med. Research Committee. Late Assist. Phys. to the Hospital of the Rockefeller Institute.

Francis Richard Fraser, M.B., 13 Drumsheugh Gardens, Edinburgh. Assist. Phys. and Assist. Director of Med. Clinic at St. Bartholomew's Hosp. Late Consult. Phys. Rhine Army. Instructor in Med. Columbia University, and Assist. in Med. Rockefeller Institute.

Charles Paget Lapage, M.D., 20 St. John Street, Manchester. Phys. Manchester Children's Hospital. Lecturer on Children's Diseases, University of Manchester.

John William McNee, M.D., D.S.O., 7 Belgrave Terrace, Glasgow. First Assist. Med. Unit. University College Hospital.

John Smyth Morrow, M.D., Ela House, Antrim Road, Belfast. Phys. Royal Victoria Hospital, Belfast.

Charles Putnam Symonds, M.D., 58 Portland Place, W. 1. Assist. Phys. and Assist. Neurologist, Guy's Hospital.

It was resolved to accept the invitation from Birmingham to hold the 1921 Meeting in that City.

It was resolved on the motion of the President, seconded by Sir Archibald Garrod, that a message of sympathy should be sent to Lady Osler in her recent bereavement, and an expression of the profound loss incurred by the Association by the death of Sir William Osler, one of its founders and most active members.

The Treasurer presented the balance-sheet, which was adopted.

SCIENTIFIC BUSINESS

1. Dr. C. H. Melland described the occurrence of *papilloedema* in a considerable proportion of cases of *epidemic encephalitis* and *encephalitis lethargica*. This was found to be present in about one-third of the number of cases (about 30) that he had met with, not only in cases of the more severe type with a considerable degree of lethargy, but also in many of the slighter cases with minor degrees of headache and pyrexia, and perhaps paralysis of one or more ocular muscles.

The question of diagnosis from other causes of increased intracranial pressure such as meningitis and cerebral tumour was discussed.

Dr. E. Bramwell stated that in not one of 57 cases he had seen was found definite papilloedema.

Sir James Purves Stewart agreed with the last speaker as to the rarity of papilloedema in polioencephalitis.

2. Dr. Donald Core, in a communication on *a psychical response and its relation to certain nervous disorders*, described observations made on movements performed by patients in response to orders. The patient told to bend forwards or backwards often made the movement the reverse to that ordered. 'Terror' neurosis cases in particular showed these or similar faulty responses.

The matter was further discussed by Dr. Hurst, Professor Drummond, and others.

3. Dr. Judson Bury discussed the *physical basis of the neuroses*. He considered that emotional disturbance might be the cause of definite organic disease and give rise to such conditions as chorea, paralysis agitans, and even jaundice. In such cases he believed there was some definite organic lesion of the central nervous system, possibly in the extra-pyramidal tracts, or some chemical change in the blood or lymph which bathed these channels.

Dr. A. Hurst stated that he saw no cases of paralysis agitans arising out of the war. That some chronic cases of neurosis do not recover he regarded as due to faulty methods of treatment, and should not be used as an argument against the functional origin of such cases. A physical element may be present in some instances, possibly

a varying resistance in the synapses, as in cases in which the pupillary response to light may have absolutely vanished, but may suddenly reappear with recovery. He regarded the war cases of Graves's disease as pseudo, not real, cases of this condition, as they were rapidly cured by hypnosis.

Sir A. Garrod pointed out that it was impossible to distinguish between Graves's disease proper and the 'pseudo' forms, as stimulation of the sympathetic might account for the symptoms in both.

Dr. Craven Moore stated that the cases of pseudo Graves's disease were due to sustained or prolonged fear, and not to wounds.

The subject was also discussed by Dr. Hobhouse, Professor Murray, and others.

4. Dr. John Hay, on the *distribution of cardiac pain*, emphasized the importance of early diagnosis of the nature of pain in cardiac disease. He related several cases of heart disease with epigastric pain, and others with pain on the right side of the chest and right arm. He questioned the origin of the pain in such cases. Was it due to the visceral organ associated with the segmental area, or to the cavity of the heart connected thereto?

Sir Thomas Horder asked on what grounds the epigastric pain in such cases should be referred to the heart and not to the abdominal aorta. He pointed out the frequency of extensive atheroma of the aorta in females, and suggested that this might account for attacks of pain in the upper part of the abdomen.

Dr. Ritchie held that the abdominal pain was not cardiac but hepatic.

The subject was further discussed by Professor Byrom Bramwell, Dr. McIlwaine, and others.

5. Dr. Tyson related a case of *Post-operative mania* after appendicectomy. Delusional insanity and melancholia were the types usually met with, and the prognosis was better in the former than in the latter. He considered that hereditary disposition to insanity was the most important aetiological factor.

From 2 to 3 p.m. Clinical Demonstrations took place in the University Buildings, and a number of interesting cases were shown.

FRIDAY AFTERNOON. 3 p.m.

1. Dr. Ashley Mackintosh related a *case of hyperplasia of the suprarenal cortex.* A boy aged 14½, with obesity, glycosuria, headaches, and marked hirsuties of eyebrows, forehead, chin, and axillary and pubic regions, which was rapidly increasing. Blood-pressure—systolic 240, diastolic 170–80. Nervous system—fields of vision and sella turcica normal. Striae atrophicae on shoulders, abdomen, and thighs. There was increasing muscular weakness, and the left lower ribs were becoming prominent. He regarded the case as one of new growth of the suprarenal body.

Sir A. Garrod had seen several similar cases, but stated that most cases of hyperplasia of the suprarenal cortex do not exhibit glycosuria. One similar case recovered after administration of thyroid extract.

2. Sir Archibald Garrod discussed *the relation of the thyroid to the pancreas.* Most of the endocrine glands act against the pancreas, the thyroid and pituitary glands in particular appear to have a 'damping' effect on this gland, and glycosuria is an indication of this action. In depancreatized dogs changes are found in the pancreas. He quoted cases illustrating this relationship—

1. Beginning with glycosuria and later developing Graves's disease.
2. Beginning with abdominal pain, then developing Graves's disease and later fatty stools: pancreatic calculi found in this development.
3. Graves's disease, with fatty stools.
4. Pancreatitis, with exophthalmos.

Professor Murray recognized the relationship and referred to a case of acromegaly with Graves's disease and diabetes. He asked if any cases of acromegaly with myxoedema had been recorded.

Sir William Hale White said that in his series of cases of definite Graves's disease 20 per cent. had some degree of glycosuria, and of these one-third had serious diabetes and died of it. He referred to two cases of fatal myxoedema, in which the thyroid was greatly hypertrophied.

Professor Byrom Bramwell also spoke.

3. Dr. Arthur Hurst, on *the so-called pernicious vomiting of pregnancy*, referred to the usual division of this condition into two classes: 1. The nervous. 2. The toxaemic. In the first the urine was normal, in the second it showed a high ammonia index. In the first the prognosis was usually regarded as good and isolation brought about recovery, whilst for the second—the toxaemic form—emptying of the uterus was generally advocated. With this he disagreed, as he did not recognize the toxaemic type. He related a case of severe vomiting in pregnancy, with a very high ammonia coefficient, in which it had been decided to empty the uterus. Treatment by suggestion, however, practically cured the patient in 24 hours. He considered psychotherapy the best form of treatment in these cases.

Dr. Langdon Brown suggested that the high nitrogen coefficient might be due to starvation, and stated the coefficient was much higher in professional fasters during their fasts than in the cases of pernicious vomiting quoted by Dr. Hurst.

Sir W. Hale White, Drs. Judson Bury, Reynolds, and Starling, and Professor Drummond joined in the discussion.

4. Dr. A. G. Gibson gave the results of *bacterial culture in splenomegaly*. Six cases were examined: five were spleens removed by operation and one *post mortem*. The spleens were all enlarged and fibrosed. Of these two gave a streptothrix, two were negative, one was tuberculous, and one gave Friedlaender's type. The streptothrix was pathogenic to monkeys but not to rabbits or guinea-pigs.

Dr. Hurst referred to a case in which the Wassermann blood reaction was positive in spite of treatment, but became negative after splenectomy. The boy, four years after operation, was now in excellent health.

5. Dr. J. A. Ryle described the method of *investigation of gastric function by means of the fractional test-meal* introduced by Rehfuss in 1914. He gave the results obtained both in healthy and unhealthy persons. For clinical investigation he regarded the method as of much greater value than the one hour test-meal, as it enabled a study to be made of the resting juice, the rate of emptying, the secretion of acid, pepsin, and mucus, and the regurgitation of bile throughout the period of gastric digestion. It also allowed of pharmacological experiment.

The method was discussed by Drs. Shaw, Craven Moore, Hurst, and Graham.

The Annual Dinner was held at 7.45 p.m. at the Midland Hotel.

The President, Dr. Judson Bury, was in the chair. There were three guests: the Lord Mayor of Manchester (F. Fox, Esq.), Sir Edward Donner, Bt., C. R. Hall, Esq., Commandant of the British Red Cross.

Eighty-seven members and guests were present.

SATURDAY, May 22nd, 10 a.m.

1. Dr. Edwin Bramwell described a series of eight cases of *myotonia atrophica*. The condition began as a myotonia, ran a slow course, and was not of itself fatal. Fibrillary tremors were not present. An atrophic condition of the testicles was not

uncommon. Developmental defects, such as persistent bronchial clefts, narrow palatal arch, infantile type of epiglottis, absence of pectoral muscles, were observed. All his cases exhibited some disorder of articulation.

In his one case with P.M. no degeneration of the posterior column was found. Cataract was present in two cases.

Sir J. Purves Stewart and Dr. Hurst agreed that the condition should be classed with the muscular dystrophies.

Professor Wardrop Griffith and Sir W. Hale White discussed its relationship to Thomsen's disease. Dr. Tidy also spoke.

2. Dr. Edwin Bramwell related a case of *frontal tumour*, with frequent fits of the Jacksonian type, *unilateral* in distribution, but preceded by *bilateral* clonic movements of the occipito-frontalis muscle. He considered that this pointed to a bilateral innervation of this muscle.

Sir J. Purves Stewart pointed out that the frontalis muscle was always bilaterally affected in fits, and also the palatal muscles.

Drs. Poulton and Hurst also joined in the discussion.

3. Professor G. R. Murray and Dr. C. Powell White described the *condition of the urine in diseases of the thyroid*. The investigation was undertaken to ascertain if changes in the urine corresponding to variations of metabolism were present in such diseases.

Professor Reynolds and Dr. Poulton criticized the results.

4. Dr. Francis Boyd discussed the *indications for the surgical treatment of nephritis*. He related two cases of nephritis in which decapsulation of the kidneys appeared to have been followed by marked improvement. In reply to a question from Dr. Lewis Smith he stated that the blood-pressure was low and retinal changes were absent in both cases.

Professor Murray and others referred to the difficulty in foretelling the cause in cases of nephritis, which so often may suddenly improve without determined cause.

Drs. Lapage, Poulton, Craven Moore, and others joined in the discussion.

5. Dr. Dingwall Fordyce related his experience of *calcium treatment in infantile spasmophilia*. A solution of 30 gr. $CaCl_2$ to one pint of water was employed, and of this 3 oz. = 4 gr. $CaCl_2$ were given subcutaneously once daily to infants, 10 gr. to older children, in diminishing doses for 7–8 days or up to $7\frac{1}{2}$ gr. intravenously. This caused a marked slowing of the pulse in a few minutes with relief of symptoms and disappearance of facial irritability in 24 hours. In infants the intravenous injections were made into the superior longitudinal sinus.

Sir Purves Stewart, Dr. Travers Smith, and Dr. Charles also spoke.

Clinical demonstrations took place in the Library from 2 to 3 p.m.

SATURDAY, 3 p.m.

1. Dr. Cowan and Dr. W. T. Ritchie discussed *the significance of the R.S.T. complex of the electro-cardiogram*. They showed a series of electro-cardiograms which presented a prolongation of the R–T interval, i. e. prolongation of the period of ventricular contraction. The significance of the condition was discussed, and the general feeling was that it was most probably due to changes in the terminal arborizations of the primitive tissue, or in the muscle itself.

2. Dr. G. B. Dowling (introduced) and Dr. E. P. Poulton related a case of *sino-auricular heart-block and its bearing on the mechanism of the heart's beat*.

This was discussed by Professor Wardrop, Drs. Griffith, Cowan, and McIlwaine.

3. Dr. W. Gordon gave a short communication on *auscultation and percussion of the heart.* He laid stress on the value of immediate auscultation in doubtful cases and on the superiority of the wooden over the binaural stethoscope in the examination of the heart. He was of opinion that for the determination of the size of the heart, percussion in the upright gave more accurate results than in the recumbent position.

He described a *test for chorea.* The patient, whilst holding the hands above the head with the palms uppermost, is told to put out the tongue. This brings out the movements in the arms and fingers.

UNILATERAL ALTERATIONS IN BLOOD-PRESSURE: THE DIFFERENTIAL BLOOD-PRESSURE SIGN

SECOND COMMUNICATION

By EDGAR F. CYRIAX

In this Journal (1920, xiii. 148–64) I published the results of 819 observations on the blood-pressures in both arms on a series of 73 cases, 72 of which were in-patients at St. Mary's Hospital. Practically all the cases examined were surgical operations and traumas, the majority being war injuries. I found that differences between the readings on the two sides were quite common; as regards the maximum pressures, differences of 10 mm. and over were found in about 83 per cent., and of 20 mm. and over in about 12 per cent. of all cases; as regards the minimum pressures, the numbers were found respectively to be about 81 per cent. and 20 per cent. To such differences I ventured to give the name of the differential blood-pressure sign.

I now present similar observations on blood-pressure on a second series of 128 cases, the total number of observations being 1,897. The cases examined were for the most part (93 cases) taken from my private practice; the remainder were in-patients at St. Mary's Hospital, namely:

Eleven cases under the care of Dr. S. Phillips.

Nine cases under the care of Mr. T. G. Stevens.

Eight cases under the care of Mr. Warren Low.

Seven cases under the care of Mr. W. H. Clayton-Greene.

I take this opportunity of thanking the above-mentioned physicians and surgeons for kindly granting me facilities for making my observations.

This second series includes both unilateral and bilateral conditions in all stages—acute, subacute, and chronic. I divided the cases into two groups: (A) Unilateral conditions, bilaterally unequal conditions, and operations performed upon structures in the middle line. The total number of cases was 56, and the number of observations was 807. This group was further divided into two divisions: (*a*) recent cases, numbering 24; (*b*) old standing ones, numbering 32. (B) Bilaterally equal (as far as could be ascertained) conditions and constitutional

disorders. The total number of cases was 72, and the number of observations was 1,090.

The same precautions and technique were employed as in the first series, as described in my first communication. When abnormally large differences were encountered, they were in almost all cases controlled by a second observation taken three minutes later.

Results.

As regards unilateral or bilaterally unequal traumatisms and operations, the results previously found, as published in my former communication, were fully confirmed. As regards operations performed upon structures in the middle line, the differential blood-pressure sign was also frequently found to occur, though not so commonly as in the former group. The sign was also encountered in a large proportion of old operations and traumatisms as well as in unilateral unoperated medical cases, and occurred almost as frequently as in the recently operated and fresh traumatic cases, excepting as regards minimum pressures of 20 and over, which occurred, roughly speaking, in the proportion of 1 : 2½.

The differential blood-pressure sign was also present in a considerable number of bilaterally equal conditions and constitutional diseases. Roughly speaking, they occurred about half as frequently as in group A. Special mention must be made of the fact that the sign was present in all spinal curvatures examined. This fact lends additional evidence in favour of the theory put forward by me (*Practitioner*, 1919, cii. 314–22) that spinal column conditions may be the starting-point of visceral disease by inducing local vaso-motor changes.

In all the tables given below the differences are calculated with reference to the right arm.

The extent of the changes encountered (excluding the first readings) were as follows:

(*a*) Maximum pressure:

	Group A.				*Group B.*	
Differences of	Division I.		Division II.			
30	0 times in	0 cases	0 times in	0 cases	1 times in	1 cases
28	0	0	0	0	0	0
26	1	1	1	1	0	0
24	0	0	2	2	1	1
22	1	1	1	1	4	3
20	5	3	5	4	5	3
18	2	2	2	2	4	1
16	5	5	8	6	13	8
14	10	5	13	7	17	8
12	11	8	25	15	23	11
10	33	18	40	20	44	20

(*b*) **Minimum pressure:**

Differences of	*Group A.* Division I.		Division II.		*Group B.*	
30	0 times in	0 cases	0 times in	0 cases	0 times in	0 cases
28	0	0	1	1	0	0
26	2	2	2	2	1	1
24	3	3	1	1	2	1
22	1	1	5	3	0	0
20	8	7	7	4	5	3
18	2	2	6	6	4	4
16	9	8	4	3	12	8
14	16	12	4	3	13	10
12	11	12	15	8	21	14
10	32	17	33	17	46	20

Considered more in detail:

Differences of 12 and upwards between both maximum and minimum (not of necessity occurring on the same day) were found as follows in group A:

No. of observations.	Maximum.	Minimum.	Nature of case.
27	+26, +24, +18, +16, +14, +12	+18, +12, +12	Chronic mucous colitis
11	+26, +20, +20, +18	−20, −18, −16, −14, −14, −12	Removal of uterus
35	+22. −20, +16, +16, −16, +14, +14, +14, +12	−28, −26, −24, +22, −22, −20, −20, −20, −20, −18, −12, −12	Fracture of left radius and left tibia
37	−20, −20, +18, −16, +14, +14, +14	+20, +14	Operation for appendicitis
6	+20, +16	+20, +14	Operation for appendicitis
8	−20, −14, −14, +12	−20	Hemiplegia of right half of the body
14	−18, −14	−12	Neuritis of left face and left arm
13	−16, −14, −12	−14, −14, −12, −12, −12	Removal of right eye
19	−16, −14	+26, −24, −16, −14, −14, +12, −12	Empyema on right side
21	−16, +12, −12, −12	+22, +18, +14	Pulmonary embolism on right side
9	+16, +12	+22, +14	Operation for torn perineum
12	+16, +12	+12	Operation for duodenal ulcer
17	+16	+14	Sciatica on right side
22	+14, +14, −14, −12, −12	−26, +16	Abscess in right axilla
30	+14, −14, +12, +12	+16, +16, −14, −14, −12	Amputation below right knee
15	+14, −14	−16	Chronic mucous colitis
42	+12, +12, +12, +12	+20, −14, +12	Traumatic left popliteal aneurysm
9	+12, −12, −12	−18, −12	Sciatica on right side
33	+12, −12, −12	−16, −16, −12, −12, −12, −12	Epilepsy, trephining on right side
20	+12, −12	−24, −20, +14, −12	Wound of left thumb
13	+12, +12	+22, −22, +12	Hemiplegia of right half of the body
9	−12	−26	Haematemesis
17	+12	−20, −20, −16, −14, −12	Right psoas abscess
6	+12	+18, +14, +12	Removal of cystic uterine tumour
21	+12	+14, −12	Arthritis (?) of left hip
5	+12	+12	Trauma of right shoulder

and in group B:

No. of observations.	Maximum.	Minimum.	Nature of case.
21	+24	+12	Syringomyelia
29	+22, +22, +20, +16, +14, +14, +12, −12	+16, +14, +12	Epilepsy
131	−22, −20, −20, −20, +18, −18, −18, −18, +16, −16, −16, −16, −16, +14, −14, −14, +12, +12, −12, −12, −12, −12, −12	−26, −24, −24, −20, −20, −18, +16, −16, −16, −16, −14, −14, −14, +12, −12, −12	Exophthalmic goitre
35	+22, +20, +16, +16, +12, +12	+14, +12, −12	Paroxysmal headache
65	−16, −14, −14, −14, −12	−16, −14, +12	Neurasthenia, vasomotor flushings
25	+16, +14, +14, +12	+16, −12	Exophthalmic goitre
17	+16, −14	−14	Scoliosis
8	−16	+18	Scoliosis
25	+14, +14, +14, +14, +12	+14, −14	Chronic infantile paralysis, both legs affected
21	+14, +12, +12	+14	Neurasthenia, goitre
53	+12, +12	+20, −16	Neurasthenia
5	+12	−18	Scoliosis
9	−12	−12	Anaemia, general debility

Differences of 12 and upwards between the maximum pressures, those between the minimum pressures in no case exceeding 10, were found as follows in group A:

No. of observations.	Maximum.	Nature of case.
5	+24, +20, +20, +16	Suspected right apical tuberculosis
12	+22, +12	Operation for right lumbar abscess
41	+20, −12	Neuritis of right arm
12	+14, +14, +14	Laryngitis, old right apical pneumonia
7	+14	Subtotal hysterectomy
23	+12	Sequellae of enteric fever and right pleurisy

and in group B:

6	+30	Scoliosis
7	+16, +14	Spastic symptoms after vertebral fracture
10	+12	Insufficient action of diaphragm
9	−12	Neurasthenia
5	+12	Chronic mucous colitis

Differences of 12 and upwards between the minimum pressures, those between the maximum pressure in no case exceeding 10, were found as follows in group A:

No. of observations.	Minimum.	Nature of case.
14	+24, −16, +12	Empyema on right side
11	−20, −14, −14, −12	Abscess in left thorax
8	−20, −12	Traumatic ankylosis of right ankle
10	−20	Neoplasm of right lung (?) pleurisy on right side
10	−18, −16	Suspected left pulmonary phthisis

No. of observations.	Minimum.	Nature of case.
27	+18, −12	Left phlegmasia alba dolens
12	−16	Empyema on right side
29	+14, +12	Right femoral thrombosis
11	+14	Fracture of right metacarpals
8	−14	Gastrojejunostomy
6	−12	Curetting and dilatation of cervix
8	+12	Empyema on left side
10	+12	Colporrhaphy, removal of cervix

and in group B:

22	−20, −20, −18, −16, −16, −14, −12, −12, −12	Chronic nephritis
31	−16, −12	Epilepsy
6	−16	Epileptiform seizures
6	−14	Neurasthenia
13	−14	Neurasthenia
22	−12, −12	Neurasthenia
13	−12	Neurasthenia
6	+12	Chronic nephritis
22	−12	Kyphosis, slight scoliosis
9	−12	Scoliosis

In the following cases no differences at all, or only negligible ones (2–4 mm.), were found:

Vertigo, presumably of syphilitic origin	1 case	Respiratory deficiency	1 case
Recovery from cerebral concussion on previous day	1	Neurasthenia	6
Old cerebral concussion	1	Neurasthenia and colitis	1
Neuritis of neck and arms	1	Neurasthenia and old mastoid operation still discharging	1
Constipation	2	Nervous breakdown	1
Constipation and vertigo	2	Arterio-sclerosis	2
Weakness of abdominal muscles	1	Chronic rheumatism in back and arms	1
Sequellae of dysentery	1	Chronic rheumatism of arms	1
Asthma	1	Lumbago	2
Suspected apical tuberculosis	1		

Conclusions.

1. The results found in surgical cases, as given in my previous communication, were fully confirmed, the only exception being that the differential blood-pressure sign was also found to occur frequently in operations upon structures in the middle line.

2. The differential blood-pressure sign is also frequently encountered in unilateral medical cases.

3. The differential blood-pressure sign is also often met with in bilaterally equal and constitutional affections. As regards the maximum pressures, differences of 10 mm. and over are found in about 35 per cent., and of 20 mm. and over in about 7 per cent. of all cases. As regards the minimum pressures, similar differences are found respectively in about 45 per cent. and 4 per cent.

4. Neglect to exclude the presence of the differential blood-pressure sign may easily lead to totally erroneous conclusions as to the state of the circulation.

NOTE. Since writing the above, I see that Mirallié (*Bull. soc. méd. d. hôp. de Paris*, 1920, xliv. 889–93) has found the differential blood-pressure sign in a number of cases of hemiplegia.

SOME OBSERVATIONS ON SUGAR TOLERANCE, WITH SPECIAL REFERENCE TO VARIATIONS FOUND AT DIFFERENT AGES

By J. C. SPENCE

(From the Medical Unit Laboratory and Children's Department, St. Thomas's Hospital)

SINCE the advent of practical methods of micro-chemical analysis, blood-sugar estimations have been established as a clinical procedure. As a result of this, much attention has been directed during the past decade to the study of the variations of the glucose content of the blood both in health and in disease. The normal level is known, and many of its physiological variations are recognized. The most important result has been a recognition of the fact that the blood-sugar of a healthy individual reacts in a definite manner to the ingestion of carbohydrate. It is known that this reaction, to which the term 'alimentary hyperglycaemia' (Bailey (16)) has been applied, becomes abnormal in the presence of certain conditions and diseases which affect sugar tolerance or interfere with carbohydrate metabolism. The changes in blood-sugar content consequent on the ingestion of carbohydrate may be expressed as a blood-sugar curve.

In the further investigation of cases of glycosuria, in the early diagnosis of diabetes mellitus and in its differentiation from renal diabetes, blood-sugar curve determinations are of undoubted value. But an extension of the test to other diseases has yielded inconsistent and contradictory results. Certain investigators have claimed that characteristic alterations of the normal blood-sugar curve occur in nephritis, cancer, affections of the ductless glands, and many other conditions. Others have claimed that in no disease is there a specific type of curve, and that its use as a diagnostic measure is of little value. Before these claims can be finally decided, it appears desirable that further investigations should be made into the factors which influence the curve in the normal person. It was for this purpose that the work described in this paper was undertaken. Experiments were carried out to determine whether the response to the blood-sugar curve test was the same at all ages, by comparing the curves of infancy and childhood with those of adult life and old age.

So much independent work has been done in different countries that a brief

[Q. J. M., July, 1921]

review of the published results may serve to show how much of the knowledge that has accrued can be accepted and put to a practical use. Baudouin (1) in 1908, and Frank (2) in 1910, estimated the blood-sugar of healthy men before and one hour after the ingestion of 100 grm. of sugar, and found it to be raised in some cases and unaltered in others. The greatest rise observed was one of 0·03 per cent. Tachau (3), in 1911, made further observations on healthy cases, and also on cases of diabetes, chronic nephritis, and jaundice. He estimated the blood-sugar at hourly intervals after the ingestion of 100 grm. of glucose. With such infrequent estimations he failed to detect the rise and fall which usually occurs within the first hour, and concluded that, in the healthy person, there was no rise in the blood-sugar after taking glucose. In each of the cases of diabetes he found hyperglycaemia after one hour. In three of the five cases of chronic nephritis which he investigated, he found no rise in the blood-sugar one hour after taking the glucose; in the other two there were rises from levels of 0·104 and 0·097 per cent. before taking the glucose, to 0·216 and 0·212 per cent. one hour later. The work of Rolly and Oppermann (4), and of Bing and Jakobsen (5), gave inconsistent results, for they also did not realize the importance of frequent estimations.

It was Jacobsen (6), using Bang's method of blood-sugar estimation, who pointed out that the blood-sugar began to rise within ten minutes of the ingestion of a meal of carbohydrate, and, reaching its maximum level within 30 minutes, the hyperglycaemia passed off in many cases by the end of the first hour. It was now evident that, if the course of the blood-sugar curve were to be accurately plotted out and used as a test of sugar tolerance, or as an indication of the functional activity of the carbohydrate storage mechanism, attention must be given to these three points: (*a*) a dose of sugar sufficient to provoke the maximum rise must be given; (*b*) estimations of the blood-sugar must be made at frequent intervals so that the highest point reached can be detected; (*c*) the estimations must be continued until the blood-sugar returns to its normal or fasting level.

Sakaguchi's (7) careful work covered this ground. Using Bang's method, he estimated the blood-sugar at intervals of ten minutes for two hours after the ingestion of 100 grm. of glucose in healthy young adults. His results are very similar to those of Jacobsen. The rise in blood-sugar was appreciable within ten minutes. It continued, reaching its maximal height within 20 to 40 minutes, and subsided quickly, returning to or below its fasting level from 50 to 90 minutes after the sugar had been taken. He found that the highest point of the curve varied between 0·133 per cent. and 0·191 per cent., but the rapid subsidence after reaching this point was constant in all his experiments. This requires emphasis, for it is this rapid return of the blood-sugar to its original level that denotes the efficiency of the carbohydrate storage mechanism; while the actual height to which the curve can rise may vary in the healthy organism with normal sugar tolerance as much as 0·050 or 0·060 per cent.

Hopkins (8), Hamman and Hirschmann (9), Bailey (10), and others by a

combination of blood and urine analyses have shown the relation between hyperglycaemia and glycosuria. There is substantial evidence in their work that in the normal adult the kidney threshold level for sugar is reached when the blood-sugar rises to a level of about 0·17 per cent.; and that it is at that level that active secretion of sugar by the kidney takes place.

This knowledge of the level of the renal threshold has been of value in investigating those cases of glycosuria to which Klemperer gave the name 'renal diabetes', and Saloman 'diabetes innocens'. Graham (11) has contributed a paper on this subject in which five cases of diabetes innocens are described. Blood-sugar estimations served to differentiate them sharply from diabetes mellitus. There was no hyperglycaemia. The blood-sugar curves were normal or lower than normal. Yet sugar was secreted actively by the kidneys. Goto (12) has reported another case. His paper contains a full review of the literature on this subject.

The use of the determination of the blood-sugar curve as a clinical test is described very clearly and fully in a recent paper by MacLean and de Wesselow (13). They compared the curves of normal adults with those of diabetics. They determined the response to various carbohydrates, using glucose, cane sugar, laevulose, lactose, galactose, maltose, and potatoes. Each of these provoked a somewhat similar rise, except laevulose, the ingestion of which had no effect upon the blood-sugar. It was shown in their experiments that a dose of 25 grm. of sugar was sufficient, in the healthy organism, to produce a maximal rise, usually from a fasting level of between 0·09 and 0·11 per cent. to a height of 0·17 per cent., and that larger doses were incapable of making the blood-sugar exceed this level, serving only to prolong slightly the descent of the curve. They enunciate the working rule that if the blood-sugar fails to return to its original level within one and a half hours after a single dose of 50 grm. of glucose, a defect in the carbohydrate storage mechanism may be considered to be present. They showed that the characteristic of the diabetic curve is that it continues to rise for two or three hours after the ingestion of glucose, and is followed by such a slow decline that at the end of four or five hours it still may be raised above the original level. In cases of severe diabetes the rise in blood-sugar may be to levels of 0·300 or 0·400 per cent., while the milder cases of diabetes would present blood-sugar curves which approximated more to those of a normal person.

This prolonged hyperglycaemia in diabetics following the administration of a dose of glucose has been noted by most of the workers on the subject, and there is general agreement as to the essential difference between the normal blood-sugar curves and those of a diabetic. But as yet no satisfactory explanation has been put forward as to why, in the healthy person, the hyperglycaemia should pass off, and the blood-sugar curve return to its original level, at a time when absorption of the glucose from the alimentary canal is still proceeding. That this is the case, absorption continuing after the normal blood-sugar curve has returned to its original level, is apparently true, for it is revealed in the

severe diabetic by the steady rise in blood-sugar which continues for two or three hours after the ingestion of glucose. The hypothesis of MacLean and de Wesselow is that the drop in the normal curve is caused by the sudden intervention of a storage mechanism, which abstracts the sugar from the blood more quickly than it enters. Hamman (14) attempted to throw light on this point. He found that the administration of a second dose of sugar immediately after the reaction of the blood-sugar to an earlier dose was complete did not cause so great a rise in the blood-sugar as the first dose. The difference between the first and second reaction was slight, but was constant in all nine cases investigated. He assumed that the first dose of glucose stimulated the mechanism of carbohydrate disposal so that the repetition of an equal dose while this mechanism was still in action produced a less marked hyperglycaemia.

It has been suggested by Fisher and Wishart (15) that this sudden fall in the blood-sugar level is due to a change in the blood volume, the osmotic effect of an increased sugar content producing a dilution of the blood. Bailey (16) investigated this point in subsequent work, and found only slight changes in the blood-volume as measured by haemoglobin estimations. Strouse (17) attempted to change the blood volume by varying the water intake, and by administering cathartics; he found that these measures had no effect on the blood-sugar level. Both of these authors conclude that the sudden fall in the curve is not the result of a change in the volume of the blood. These conclusions are probably correct, for did the fall in the blood-sugar percentage depend on this factor, it would mean that in some cases a dilution of a hundred per cent. or more must take place; for a rapid fall from 0·18 to 0·09 per cent. is frequently seen.

Whatever the fundamental significance of this transient rise in the blood-sugar after the ingestion of carbohydrate may be, there is a consensus of opinion as to the value of a determination of the shape of the blood-sugar curve, which portrays this rise, in the diagnosis and prognosis of cases of diabetes mellitus. The height and the length of the curve are an index of the severity of the disease. Conditions other than diabetes have been described in which variations of the normal curve may occur. A perusal of the published work shows, however, that in none of these are the variations so gross or so constant as in advanced diabetes, although some of them may resemble closely the type of curve found in mild cases of diabetes.

Nephritis. Chronic interstitial nephritis is one of the conditions in which hyperglycaemia and a prolonged blood-sugar curve has been frequently reported. The type of curve which has been described in many cases is one with an original fasting blood-sugar level of between 0·12 and 0·16 per cent., mounting slowly after 100 grm. of glucose to reach a height of 0·20 to 0·25 per cent. in from one to one and a half hours, and subsiding slowly to regain its original level about three hours after the first estimation; a curve closely analogous to that of a mild diabetic. There are, however, many cases of chronic nephritis on record with normal blood-sugar curves. Thus hyperglycaemia cannot be looked upon as a *sine qua non* in this disease. Tachau (3) examined five cases of

chronic nephritis and found normal blood-sugar levels in three of them; in the other two the blood-sugar was still raised above 0·200 per cent. one hour after the ingestion of 100 grm. of glucose. Hopkins (8), using Bang's method, found a moderate hyperglycaemia in many of those cases of nephritis with a low sulphothalein elimination. Some of the 26 cases he investigated had normal blood-sugars. Bailey (16), using Lewis and Benedict's method, reported a case of chronic interstitial nephritis in which the blood-sugar curve after 75 grm. of glucose rose from 0·15 per cent. to 0·36 per cent., regaining the original level in four hours. He noted that hyperglycaemia was greatest in those cases of diabetes which were complicated by chronic renal disease.

Hamman and Hirschmann (9) studied the blood-sugar curves in six cases of nephritis. In each of these the hyperglycaemia after 100 grm. of glucose was abnormal, the blood-sugar being still raised after two and a half hours.

There seems to be sufficient evidence for the belief that in many cases of nephritis the reaction to the blood-sugar curve test may simulate that found in mild diabetes, but no discussion of the results found in the work on which this evidence is based would be complete without reference to the experiments reported by de Wesselow (18). He has shown, by comparing the picric acid method of blood-sugar estimation of Lewis and Benedict with MacLean's method, that the former may give readings 40 to 50 per cent. too high, and that these may be the result of the presence of creatinin in the blood which, under the conditions of the estimation, gives a colour similar to that produced by glucose in the presence of picric acid. Cowie and Parsons (19) have confirmed this work, and state that epinephrin, acetone, diacetic acid, and creatinin, when present in the blood, will vitiate the results given by the Lewis-Benedict method of estimation and its modifications. If this be so, then in those cases of nephritis in which there was retention of creatinin with other nitrogenous substances, the picric acid methods of estimation would show an apparent rather than a real hyperglycaemia.

Diseases of the ductless glands. An application of the blood-sugar curve test to cases in which there was disease of the ductless glands has yielded a few isolated results which are very suggestive. But viewed as a whole the results are extremely indefinite and contradictory. Croser Griffith (20) has reported a case of the hypopituitarism of Fröhlich with a blood-sugar curve of increased sugar tolerance. One hour after 100 grm. of glucose had been given by the mouth the blood-sugar level was 0·104 per cent. and there was no glycosuria. After two months' treatment with pituitary extract sugar tolerance was diminished, and an altered blood-sugar curve resulted. A reading of 0·18 per cent. one hour after 100 grm. of glucose was now obtained, and sugar was passed in the urine. Bailey (10), on the other hand, has reported a case of hypopituitarism with a prolonged hyperglycaemic blood-sugar curve. Janney and Isaacson (21) have reported a case of acromegaly with a prolonged curve of the diabetic type. They also investigated cases of exophthalmic goitre, cretinism, and myxoedema. The results of this work, when grouped with the results reported in a later paper by

Janney and Henderson (22), show that, so far, it has been impossible to demonstrate by the use of the blood-sugar test any constant relation between the functional activity of the thyroid gland and sugar tolerance. Many of the curves both in exophthalmic goitre and in myxoedema were normal.

McCrudden and Sargent (23) hold that there is persistent hypoglycaemia in muscular dystrophy.

Cancer. A number of observations on the blood-sugar levels in cases of cancer and other malignant growths have been reported by workers in America. A high prolonged curve has been described as being present in many cases; but, as in nephritis, a number of cases with normal blood-sugar curves have been recorded. Benedict and Lewis (24), in an investigation carried out on 53 cases of malignant growth, found that in 10 of these the blood-sugar was still raised three hours after a carbohydrate meal.

Fredenwald and Grove (25), using Epstein's method, claim to have found a characteristic and constant deviation from the normal blood-sugar curve in cancer. In 32 cases of cancer of the gastro-intestinal tract they estimated the blood-sugar before a dose of 100 grm. of glucose, and 45 minutes and 120 minutes later. They found a high initial level, which after 45 minutes was 0·24 per cent. or higher, and remained at this level for at least two hours, showing no tendency to subside during this time. This they termed the 'cancer curve'. They concluded that the blood-sugar curve test was a valuable aid to diagnosis in cases of carcinoma. There was wide variation in their actual readings. The fasting blood-sugar levels in the 32 cases lay between 0·120 and 0·384 per cent. In 11 of the cases the blood-sugar rose above 0·250 per cent., and yet only one of these showed any glycosuria during that time. This unusual feature would appear to indicate either that the renal threshold for sugar was considerably raised in all these cases, or that the method of estimation tended to record readings that were much too high.

Rohdenburg, Bernhard, and Krehbiel (26, 27) contributed two papers on this subject. In the first their results in 24 cases of carcinoma agreed substantially with those of Fredenwald and Grove, a high prolonged curve of the diabetic type resulting. However, in the second paper they modified their views after finding normal blood-sugar curves in about half the cases investigated. They conclude that there is no type of blood-sugar curve that can be considered as characteristic of cancer, but that hyperglycaemia and a delayed curve are often present in that condition.

Chronic arthritis. Pemberton and Foster (28), in a study of cases of chronic arthritis occurring in the American Army, noted that the severest cases had a diminished sugar tolerance and showed an abnormal response to the blood-sugar curve test. Using the Benedict modification of the Lewis-Benedict method, they then carried out a routine examination of these cases in the stages of marked severity, of convalescence, and of recovery when such resulted. They found that, when the disease was at its worst, there was usually a hyperglycaemic delayed curve, and that in those cases which were improved or cured by the

removal of foci of infection such as septic tonsils and carious teeth, a normal blood-sugar curve was restored. They advance the theory that many of the diabetic type of curves, that have been described in various diseases other than diabetes, may be the result of some unrecognized septic focus.

The response of infants and children to the test has been studied mainly by German workers. Mogwitz (29), in six children between the ages of 4 months and 13 months, found that their fasting blood-sugar levels were the same as those of adults. The blood-sugar curve was determined in these cases after feeding them with milk which provided about 2 grm. of sugar per kilo of body weight. In four of these cases there was but little response, the blood-sugar curve rising at the most 0·02 per cent. after half an hour. The highest points in the rise of the other cases were 0·124 per cent. and 0·134 per cent.

Frank and Mehlhorn (30) experimented on 18 children under the age of 3. They gave to them 8 grm. of saccharose per kilo of body weight. In 8 of the patients glycosuria resulted; in two of these the renal thresholds were at 0·130 and 0·160 per cent., which are considerably below those usually given for an adult.

Bergmarck (31) investigated the response of the blood-sugar to the ingestion of various sugars in infants. He claims that saccharose produced a higher response than maltose and maltose a higher response than lactose. But all the resultant curves were much lower than those of adults. The average maximal response to doses of glucose in infants under 12 months was a rise to 0·130 per cent.

Methods.

Most of the experiments recorded in this paper were carried out five to six hours after a light breakfast. This, in the normal individual, is a sufficient period of fasting to allow the influence of the previous meal to pass off. The amount of carbohydrate given varied according to the age of the patient. To adults 50 grm. of glucose dissolved in 200 c.c. of water was usually given. This is sufficient, as MacLean and de Wesselow have shown, to provoke the maximal response, and larger doses need not be given. The amount given to the infants was roughly 2 grm. of sugar per kilo of body weight. In older children the proportion was less.

MacLean's (32, 13) method of blood-sugar estimation was used throughout. The advantages of this method are well known. Capillary blood is collected in a 0·2 c.c. pipette from a prick in the finger in adults, or from the lobe of the ear or the heel in children. Thus the necessity for venous punctures, which many of the other methods entail, is avoided, and blood can be obtained with great frequency with the minimum of discomfort to the patient. The experimental error was very slight, as will be seen from the following figures.

These are duplicate readings in the case of a man who was given 50 grm. of glucose. Both pipettes were filled simultaneously from the same drop of blood.

	(1)	(2)
Blood-sugar before glucose (1 p.m.)	= 0·088 per cent.	0·090 per cent.
,, ,, ½ hour later (1.30 p.m.)	= 0·213 ,,	0·210 ,,
,, ,, 1 hour later (2 p.m.)	= 0·190 ,,	0·190 ,,

The accuracy of the method and the constancy of a healthy person's blood-sugar level under fixed conditions are illustrated in the following figures.

On eight days extending over a period of three weeks, blood was taken from the same individual at the same hour in each day. In each case it was four hours after a light breakfast. The results were:

22.12.20.	= 0·089 per cent.
30.12.20.	= 0·095 ,, ,,
31.12.20.	= 0·098 ,, ,,
3. 1.21.	= 0·091 ,, ,,
6. 1.21.	= 0·092 ,, ,,
10. 1.21.	= 0·098 ,, ,,
12. 1.21.	= 0·096 ,, ,,
14. 1.21.	= 0·089 ,, ,,

MacLean's method has proved so satisfactory in our hands that Cole's (33) modification of it has not been used. This modification, for which the author in the recent edition of his text-book appropriates the name 'Cole's method of blood-sugar estimation', is slight, and, as he admits, the principle of the original method is retained. Cole's so-called 'modification' does not appear to be any improvement on the original method as described by MacLean; in fact it is difficult to see wherein the necessity arose to replace the original simple and accurate method by his more or less cumbersome changes, which, without enhancing the delicacy of the method, have rendered it much more difficult to carry out.

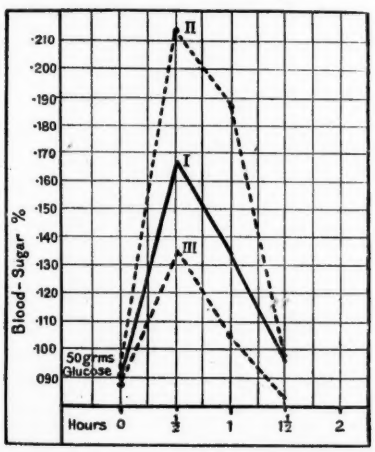

CHART I. Blood-sugar curves of normal young adults after the ingestion of 50 grm. of glucose. I = average of six cases; II = highest curve found; III = lowest curve found.

The Blood-sugar Curve in Healthy Young Adults.

In Chart I the normal curve of a young adult is given. This curve represents the average of results which were obtained from six healthy men between the

ages of 25 and 39, following the ingestion of 50 grm. of glucose. This confirms the findings of many of the authors whom we have quoted. The rise is rapid to a level of about 0·17 per cent., and the return to the original level is complete within one and a half hours. We shall use this as a basis for comparison with other curves to be described. The highest and the lowest curves which were obtained in this series of six cases are also given. They illustrate the point that, whereas the actual height attained by the curve in the normal person is variable, the time required for the return to the original level to take place is more constant.

The Blood-sugar Curve in Children.

The results obtained in an investigation of the curves in infants under 12 months of age are given in Table I, and represented graphically in Chart II. The amount of carbohydrate given was considered to be equal to the amount the

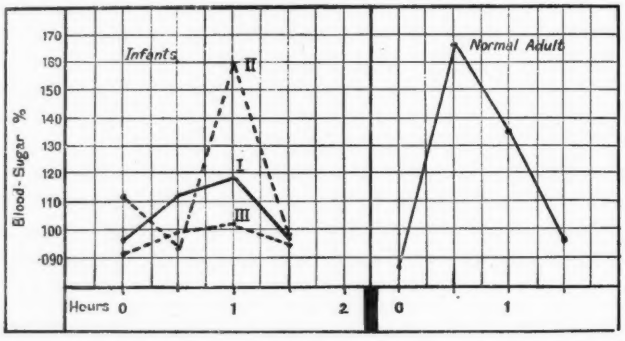

CHART II. Comparing blood-sugar curves of infants with a normal adult curve. I = average of curves of nine infants; II = highest curve found; III = lowest curve found.

infant would receive in an ordinary feed, and thus sufficient to provoke the maximum response in the blood-sugar. Here again, the average of the results of all the experiments in this group has been taken, and the curves represent the average and the highest and lowest findings of the series. A comparison of these with the normal adult curve reveals a marked difference. As a general rule it appears that the younger the infant the less the hyperglycaemia following the ingestion of sugar. This would suggest how active the carbohydrate storage mechanism is in very young children. The rate at which the infant is fed must be taken into account, for if the milk or sugar solution were ingested slowly over a period of 20 to 30 minutes, the rate of absorption might never be great enough to effect a sudden rise in the blood-sugar. But in these cases attention was paid to this point. The sugar solution was swallowed rapidly in from five to ten minutes.

In two of the cases (J. C. and A. D.) lactose produced a more pronounced rise than saccharose and glucose, both of which appear to be absorbed and assimilated readily.

TABLE I.

Name.	Age.	Weight in Kilos.	Amount of Sugar taken.	Blood-sugar %. Before taking Sugar.	½ Hour after.	1 Hour.	1½ Hours.
B. D.	6 days	4	80 c.c. of breast milk = 5 grm. lactose	0·088	0·112	0·103	0·089
L. G.	2 weeks	3½	7·5 grm. lactose	0·080	0·094	0·110	0·098
C. B.	6 weeks	3	10 grm. glucose	0·094	0·140	0·139	0·112
—	10 weeks	4½	7·5 grm. glucose	0·098	0·110	0·105	0·090
S. R.	4 months	6	100 c.c. cow's milk + lactose = 9 grm. lactose	0·092	0·097	0·101	0·097
J. C.	8 months	7½	15 grm. saccharose	0·098	0·117	0·092	0·103
,,	,,	,,	15 grm. lactose	0·112	0·093	0·160	0·096
A. D.	8 months	8	8 grm. lactose	0·108	0·127	0·149	0·098
,,	,,	,,	10 grm. glucose	0·098	0·114	0·107	0·097

In Table II the results obtained in children between the ages of 2 years and 7 years are given. The response in these is much greater than that which was found in infants; and in children above the age of 3 years it appears to be similar to that found in young adults. The normal adult curve can be taken, therefore, as representing the rise which occurs in all children above that age, and any variation from this would indicate an alteration in carbohydrate tolerance.

The results found in the cases of rickets, encephalitis, muscular dystrophy, and diabetes are also given. The case of diabetes was a boy aged 7 (E. F.), whose blood-sugar had been reduced to a normal level by a diet of limited carbohydrate. A typical diabetic curve followed the ingestion of 25 grm. of glucose. The case of rickets (C. D.), and the case of encephalitis lethargica (A. W.), had a diminished carbohydrate tolerance. In both the curve was prolonged, the blood-sugar being raised considerably one and a half hours after the dose of carbohydrate had been taken.

TABLE II.

Name.	Age in Years.	Amount of Sugar taken.	Blood-sugar %. Before taking Sugar.	½ Hour after.	1 Hour after.	1½ Hours after.	Remarks.
A. G.	4	15 grm. glucose	0·106	0·187	0·131	0·100	Healthy
B.	4	20 grm. glucose	0·094	0·150	0·106	—	,,
R. S.	2	15 grm. glucose	0·105	0·141	0·135	0·090	,,
,,	,,	15 grm. lactose	0·094	0·122	0·103	—	,,
C. S.	3	20 grm. saccharose	0·097	0·152	0·103	0·093	,,
J. T.	7	Carbohydrate meal = 35 grm. sugar	0·111	0·134	0·114	0·080	,,
C. D.	2	15 grm. glucose	0·083	0·155	0·161	0·140	A severe case of active rickets
A. W.	6	Carbohydrate meal = 25 grm. sugar	0·089	0·134	0·219	0·170	A case of encephalitis lethargica with occasional glycosuria
H. S. C.	7	20 grm. glucose	0·112	0·222	0·117	—	A case of muscular dystrophy
E. F.	7	25 grm. glucose	0·103	0·190	0·212	0·260	A case of diabetes mellitus

The Blood-sugar Curve in Old Age.

In Table III the results obtained in five old men over 60 years of age are given. All of them were apparently healthy, with normal cardio-vascular and renal systems. In each case the experiment was carried out after five hours' fasting; and a dose of 50 grm. of glucose was given. In Chart III the curve of the average of these results is shown and compared with the normal adult curve. The persistent hyperglycaemia and diminished carbohydrate tolerance of four of these cases (N. B., R. L., W. B., J. L.) is striking, and shows how the carbohydrate storage mechanism tends to become impaired as age advances.

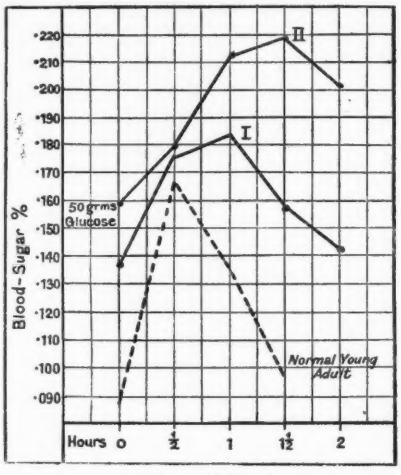

CHART III. Blood-sugar curves in old age following the ingestion of 50 grm. of glucose. I = average of curves found in five old men; II = highest curve found (no glycosuria resulted in this case).

TABLE III.

Name.	Age.	Amount of Sugar taken.	Blood-sugar %. Before taking Sugar.	½ Hour after.	1 Hour after.	1½ Hours after.	2 Hours after.	Remarks.
N. B.	62	50 grm. glucose	0·158	0·177	0·212	0·219	0·201	Dyspepsia
R. L.	77	„ „	0·149	0·197	0·168	0·125	0·109	Healthy
W. G.	74	„ „	0·110	0·125	0·130	0·125	0·098	Healthy Convalescent after minor operation
W. B.	75	„ „	0·117	0·210	0·188	0·148	0·156	Healthy Convalescent after minor operation
J. L.	71	„ „	0·149	0·160	0·198	0·170	0·162	Healthy

It is significant that the only cases, which had a normal fasting level, were two (W. G., W. B.), who were in hospital convalescing from minor operations, and on a limited carbohydrate diet. The other three, with no restriction of their diet,

appeared to be living in a state of persistent hyperglycaemia. Since this is a condition that can be easily corrected in most cases by a slight modification of the diet, its early recognition by means of blood-sugar estimations would be of value. Rational advice as to the mode of life to be pursued could then be given.

The Blood-sugar Curve in Cancer.

Four cases of cancer were investigated, and the results are given in Table IV. It will be seen that in one of these (C. B.) there is marked diminution in carbohydrate tolerance. The curve is prolonged and resembles that found in mild diabetics. Two of the cases (B. W., N. N.) present normal blood-sugar curves.

Thus we have been unable to confirm the findings of Fredenwald and Grove, who maintain that a specific type of delayed hyperglycaemic curve is present in this disease. The occurrence of one high prolonged curve in these four cases is no greater incidence than would probably be found in four cases of the same age not affected by cancer, as reference to the results in Table III will show. Both cases with normal blood-sugar curves were comparatively young and in fairly good condition.

TABLE IV.

			Blood-sugar %.					
Name.	Age.	Amount of Sugar taken.	Before taking Sugar.	½ Hour after.	1 Hour after.	1½ Hours after.	2 Hours after.	Remarks.
C. B.	54	50 grm. glucose	0·154	0·172	0·175	0·213	0·197	A case of carcinoma of colon with secondary deposits in the liver
G. W.	64	„ „	0·102	0·144	0·180	0·13 3	0·089	Carcinoma of colon
B. W.	30	„ „	0·092	0·188	0·130	0·104	—	Carcinoma of colon (colotomy)
N. N.	38	„ „	0·098	0·176	0·120	0·102	—	Carcinoma of lip

Summary.

In these investigations it has been shown that the same degree of sugar tolerance is not constant at all ages. It is greatest in infancy, and tends to become lessened as age advances. Of the five men over 60 years of age who were examined, four showed a marked diminution of carbohydrate tolerance with consequent hyperglycaemia.

In children under 3 years of age a low blood-sugar curve must be taken as the expression of the normal sugar tolerance. In children above that age the blood-sugar curve resembles that of a young adult.

In cases of cancer the sugar tolerance was variable. It was normal in the younger and decreased in the older patients.

This suggested that the hyperglycaemia and decreased sugar tolerance, which have been described in some cases of nephritis and in cancer, are due to the hyperglycaemia of old age, which is so frequently present even in apparently healthy old people.

A decreased sugar tolerance was found in a case of active rickets, and in a case of encephalitis lethargica.

This research was made possible by the grant of the John and Temple Research Scholarship, to the donor of which the writer wishes to express his gratitude. He would also express his indebtedness to Dr. MacLean, Director of the Medical Unit, in whose laboratory the work was carried out, and to Dr. Jewesbury, who allowed the use of the patients in his wards.

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INCIDENCE OF INFECTIONS WITH PFEIFFER'S BACILLUS BEFORE, DURING, AND AFTER THE 1918 EPIDEMIC

By J. W. McLEOD, A. G. RITCHIE, and C. A. DOTTRIDGE

The observations to be recorded below are in many respects incomplete, and in view of the large number of papers which have already been written on the subject of influenza it is desirable to explain at the outset the reasons which seem to us to justify this publication. In the first place, the observations, though small in number, were made at various periods from the outset of the epidemic till 1920, and the same technique was employed throughout; whereas most publications on the subject have referred to investigations carried out during some shorter period or with varying technique. Secondly, some of the observations relate to cases seen at the very outset of the epidemic, and it is in regard to the incidence of Pfeiffer's bacillus in the early stages of the summer epidemic of 1918 that there appears to be most diversity of opinion.

An extensive review of the bacteriology of influenza has recently been published by Fildes and McIntosh (1). These authors make out a strong case for Pfeiffer's bacillus as the cause of epidemic influenza. In developing this conclusion they summarize the published evidence for the existence of a filter-passing virus and show that it is decidedly weak. They also review the records of experimental evidence for the selective action of *B. Pfeiffer* toxin on the pulmonary tissues, which have rapidly accumulated in the last two years.

There is, however, no detailed comparison in their review of the incidence of Pfeiffer's bacillus during the years preceding the epidemic with that in the epidemic period.

The observations of the epidemiologists go to show that there is something like a ten-year cycle in epidemic influenza, a heavy incidence having been noted in 1869, 1879, 1890, and 1898, but not apparently between that period and the recent epidemic (Stallybrass (2)).

If Pfeiffer's bacillus is the cause of influenza, it is to be expected that the investigations recorded with regard to its incidence should show a gradual diminution of infections due to that bacillus in the years following an epidemic, and a gradual increase in infections due to it in the years immediately preceding an epidemic. We have tried to get information on these points from the literature. Unfortunately the relatively small number of investigations recorded in which Pfeiffer's bacillus has been carefully sought in the absence of influenza epidemics,

the varying competency of the investigators, and the variety of culture media chosen are all factors which make it difficult to reach a very certain conclusion.

It is well, however, to examine carefully such findings as have been recorded and to analyse as far as possible their significance.

Fortunately Tedesko (3) has published a very extensive collection of observations relating to the incidence of infections due to Pfeiffer's bacillus between the years 1896–1906. This author points out that the incidence of infections due to that bacillus, as determined by P.M. observations and by examinations of the sputum during life, rose steadily to a maximum in the years 1899 and 1900, and then fell away rapidly till in 1905–6 there were only 5–6 P.M.'s per annum in which Pfeiffer's bacillus was found, as compared with 90 in the year 1900.

Since these observations were made throughout with the same technique, and are therefore comparable, the conclusion may be drawn with some confidence that in the area to which they relate—the southern part of Central Europe—there was an epidemic prevalence of *B. influenzae* infections on a small scale about the beginning of this century; and further, that the incidence of infections with Pfeiffer's bacillus diminished in the following years, and had become almost negligible when the series of observations was terminated in 1906.

Table I gives a summary of the principal recorded observations on the incidence of Pfeiffer's bacillus in the period between 1900 and the first winter of the European war. The data are rather slender, but so far as they go they suggest the following ideas:

1. That in Europe the incidence of Pfeiffer infections was low throughout this period, although there were probably some localized epidemics like that recorded by Scheller (10) and nearly corresponding to the period of the suggested ten-year cycle.

2. That in America, although no epidemic with a high incidence of Pfeiffer infections is recorded, yet there appears to be, in certain areas at all events, a rather high endemic rate of infections with Pfeiffer's bacillus in chronic bronchitis.

3. That there seems to be little doubt that amongst children a high percentage of infections with haemoglobinophilic bacteria, whether *B. Pfeiffer* or not, is the rule in all conditions associated with catarrh of the respiratory tract.

4. That taking into account the rather scanty observations available on normal individuals, and those on cases of pulmonary tuberculosis, one can probably fix the percentage of carriers of Pfeiffer's bacillus in a population which has not been recently visited by an influenza epidemic, as between nil and 10 per cent.

In Table II we have summarized all records of infections with Pfeiffer's bacillus between the first winter of the war and the outbreak of the 1918 epidemic which we have been able to find. A comparison of the two tables brings out at once certain contrasts. These are: first, that a much larger number of localized epidemics of 'influenza', bronchitis, or atypical pneumonia associated with *B. Pfeiffer* infection was recorded between 1915 and 1918 than in the

preceding years; second, that the figures for incidence of Pfeiffer's bacillus in connexion with influenza were higher in these epidemics than in any recorded in the previous ten years, except that reported by Scheller (10) at Königsberg in 1907; third, that the contrast between the figures before and after 1915 is not found in the American as in the European publications.

To take up now the question of incidence during the epidemic. Many bacteriologists failed to find Pfeiffer's bacillus in the early summer epidemic, but its presence in a high percentage of cases was reported in areas wide apart and by observers who were altogether independent of one another, e.g. Meunier (31) and Krumbhaar (32) in France; Matthews (33) in London: von Bergmann (34) and Dietrich (35) in Germany. The almost constant presence of *B. influenzae* in the early stages of the disease during the autumn epidemic is now generally admitted, and it need not therefore be further discussed.

A further contrast between the epidemic and pre-epidemic periods can be made in the incidence of Pfeiffer's bacillus amongst the healthy population. Observations of this kind do not appear to have been numerous, but they coincide pretty nearly. Thus, Pritchett and Stillman (36) found amongst 177 normal individuals, 41 per cent. carriers; Fildes (1 and 37) found from 18 per cent. to 64 per cent. of carriers on different occasions; Cummins (38) quotes the very extensive observations made in the Medical Corps, U.S. Army: out of 2,179 persons examined 595, or 27 per cent., were found to be healthy carriers.

Lastly, there are one or two observations available giving the incidence of *B. Pfeiffer* in the throats of normal individuals in 1920, i. e. after subsidence of the main epidemic. Thus Edington (39) found that the carrier rate amongst troops after the subsidence of a small localized epidemic was 6 per cent.; while Sellers and Lepage (40), examining the naso-pharynx of children with chronic naso-pharyngeal catarrh, found four carriers of *B. influenzae* amongst 101 children.

The foregoing data may therefore be summarized as follows: In so far as the records can be trusted, they lead to the general conclusions that Pfeiffer infections, after remaining infrequent for many years, were noticed in numerous localized epidemics from 1915 onwards, till during the epidemic of 1918 the great majority of the patients attacked, and also a very considerable percentage of healthy contacts, were found to be infected with Pfeiffer's bacillus; but that with the disappearance of the epidemic the incidence of Pfeiffer's bacillus in the respiratory tract of healthy individuals has notably diminished.

We can now proceed to record our own observations, and to note how far they fall into line with the above summary of the relationship of Pfeiffer's bacillus to epidemic influenza. We have unfortunately no record of the incidence of Pfeiffer infections amongst healthy individuals prior to the 1918 epidemic. In February 1917, however, one of us saw a case which very definitely supported the impression derived from the literature that there were many localized influenzal epidemics in that year. The case was seen owing to the kindness of Capt. Hoskin, of 29 C.C.S., under whose care the patient was. This officer's

attention had been specially drawn to the fact that he was receiving case after case, many of them coming from one regiment, all of which presented somewhat similar features—namely, continuous fever, fine bronchitis, and nephritis: amongst these there was a very heavy mortality. The patient in question died after ten or eleven days of continuous fever associated with bronchitis, anasarca, occasional uraemic convulsions, and haematuria. At post-mortem it was found that there was a capillary bronchitis throughout both lungs, associated with uniformly distributed and almost confluent patches of broncho-pneumonia. There was no pleural exudate, but a number of sub-pleural petechiae, and the kidneys showed a very marked haemorrhagic nephritis. Films taken from the lung tissue showed an abundant exudate of polymorphonuclear leucocytes, and about one in every ten of these was loaded with fine Gram-negative bacilli. The lung juice inoculated copiously to ordinary agar gave very fine but numerous colonies of Pfeiffer's bacillus in pure culture. This case is interesting in two respects: first, it was in all probability one of a group of Pfeiffer infections, since the other cases had closely resembled it in their clinical features; but unfortunately the epidemic was nearly at an end when this case was seen, and opportunity for investigation of a series did not occur. Secondly, the kidney lesion, a markedly haemorrhagic nephritis, had been rare amongst the cases of so-called 'war nephritis' seen up to that time, and the tendency shown by Pfeiffer's bacillus to produce haemorrhagic lesions is well recognized; further, the intimate and dangerous relationship between influenza and nephritis has been emphasized since by Symonds (41), and in the report of the Influenza Committee to the D.G.M.S., France (42). Histological preparations from the lung showed in a marked way the infiltration of the walls of the small bronchioles with plasma cells, which has been described by Hübschmann (43) in his careful histological study of the lungs from the cases which he examined in the influenza epidemic at Leipzig in 1915. This case can probably be taken as an example of the subacute Pfeiffer lesion and contrasted with the acute or fulminant one met in the course of the general epidemic, when the bacillus had presumably reached the zenith of its virulence.

Observations on the Summer Epidemic, 1918.

The first cases coming under our observation in May had rather prominent gastric symptoms, and an investigation of them as possible cases of food poisoning was required. The clinical resemblance to influenza was soon obvious, however, and attempts to demonstrate *B. influenzae* were successful when the sputum of the first patient seen with a bronchial complication was examined by cultivation on human blood agar.

After a number of further investigations with various media had been made it was found that although isolation and preservation of the bacillus were difficult on human blood agar, yet with rabbit's blood agar it was easy to obtain profuse growths. This medium was therefore adopted as appropriate for an investigation of a series of cases to determine the incidence of infection with

Pfeiffer's bacillus. (It is notable that those investigators who have used blood other than human for preparing their media have usually recorded a high percentage of positive findings, Tables I and II. Little and Williams (44) recommend a rabbit's blood medium, and it is certainly as good as the altered blood media.)

A series of twelve cases was examined, and each was carefully charted and recorded. The clinical description of our cases written at the time when they were under observation ran as follows: The onset was sudden in all cases, and at the commencement there was constantly a complaint of frontal headache and muscular pains. In two only of the twelve cases there were diarrhoea and vomiting at the outset, which ceased in a few hours. The pains and headache diminished as the pyrexia fell. Coryza and pharyngitis were present in all, but only four showed bronchitis, and in one only amongst these was it severe. The fauces were injected and the uvula reddened and oedematous, with a covering of stringy mucus, but no enlargement of the tonsils was observed. There was no definite evidence of cardiac enfeeblement or of post-influenzal depression when those patients got about again after a few days. The temperature rose sharply at the outset, but had returned to normal by the third day in all cases except those in which the condition of the patient was complicated by a second lesion, e. g. a chronic urethral discharge; in these cases the subsidence of the temperature was more gradual.

Pfeiffer's bacillus was detected in eight of these cases (66 per cent.), and as this examination was often made when the patient's temperature had already returned to normal, the percentage infected was obviously high.

The clinical record of these cases has been given in detail because it seems probable that the statement so often made, that epidemics of influenza occur in which *B. Pfeiffer* is not found, depends upon the fact that clinical differentiations of catarrhs of the upper respiratory passages have not been carefully enough worked out in connexion with the bacteriological findings. In this connexion the findings of Edington (39) are very instructive. He examined four separate small epidemics amongst troops in 1920; in three of these *B. Pfeiffer* was found almost in every case, but in the fourth it was absent; it was then found on closer examination that the clinical histories in the cases from the fourth epidemic differed in some respects from those recorded in the other three. The two chief features by which Edington distinguished clinically between the true and spurious influenza cases which he observed were the presence of eye symptoms and the slight involvement of the throat in the latter. In both these respects, therefore, our cases correspond with those in which Edington found Pfeiffer's bacillus, i. e. they had no eye symptoms, but rather marked involvement of the throat.

Observations on the Carrier Rate at the Height of the Early Summer Epidemic.

Two dozen chronic venereal cases, otherwise in ordinary health, were examined by preparation of cultures with swabs taken from the naso-pharynx. Eight of these,

i. e. 33 per cent., were found positive. The number of cases, of course, is too small to yield an accurate figure, but it corresponds pretty closely with the observations of others with regard to the carrier rate during the epidemic period.

Period of the Autumn Epidemic.

For a variety of reasons we were prevented from making any observations on the percentage incidence of infections by Pfeiffer's bacillus at this period. One post-mortem observation seems to us to be worth noting.

The patient, a Canadian officer, went to sleep without special complaint one night; in the morning he was found unconscious in his bed, and as the troops had just crossed the frontier into Germany it was suspected that there had been foul play, and that he had been poisoned with coal-gas. He died shortly after reaching hospital at Spa, and within twenty-four hours of the time when he was found unconscious. A post-mortem examination revealed the pulmonary lesion characteristic of fulminant influenza, i. e. haemorrhagic oedema of the lungs with, here and there, little yellow-white specks. Cultures from the cut surface of the lungs showed *B. Pfeiffer* in abundant and almost pure culture. Owing to the fact that the laboratory was constantly moving at this time no attempt to prepare histological sections was made, but the lesion corresponds to that of acute influenza as described by Tytler, Jones, and Dobbin (45), and also by Menétrier (46). The lesion described by Menétrier is identical with that described above; it occurred in a rather less fulminant although very rapidly fatal case. *B. influenzae* was recovered in pure culture, and Menétrier, although he does not accept the conclusion that Pfeiffer's bacillus is the cause of influenza, maintains that the lesion described is that of Pfeiffer's bacillus. Tytler, Jones, and Dobbin state that diffuse haemorrhage with oedema was characteristic of the most acute cases, and, apart from staphylococci, which were found as often, but in smaller numbers, *B. Pfeiffer* was much more common than any other bacterium in these cases.

It is very difficult to sustain the theory that *B. Pfeiffer* is merely a secondary invader in such a case, since you have associated: first, the type of lesion recognized as characteristic of Pfeiffer's bacillus; second, the bacillus itself predominant and abundant in the lung; third, an invasion of the tissues, as rapidly followed by death as is known in any disease.

It may, of course, be maintained that this case only illustrates the fact that during an influenza epidemic, due to some virus as yet unrecognized, the virulence of all bacteria commonly found in the respiratory tract is raised. This is not strictly accurate, however, for lesions of the kind described are rarely, if ever, met, except during epidemics of influenza, whereas the pneumococcal and streptococcal lesions met in influenza epidemics are commonly seen in non-epidemic periods.

Observations on Cases showing Pulmonary Complications in March, 1919. The Third Epidemic Wave.

The investigations were unfortunately cut short, but, of 15 sputa examined, 12, i. e. 80 per cent., showed *B. Pfeiffer* in culture, and in more than half of these it was very abundant and the predominant bacterium. A number of post-mortem observations were also made at this time; no fulminant cases such as had occurred in the autumn epidemic were seen in this series. The patients died after 7–12 days' illness, and suppurative pneumococcal, streptococcal, and staphylococcal lesions predominated, although here and there an influenzal broncho-pneumonia, with *B. Pfeiffer* predominant, was observed.

If Hübschmann's (43) conclusions are sound, the deaths in this third epidemic wave were mainly due to the facilitation of invasion of the lung by varied micro-organisms, which results from previous Pfeiffer lesions. He considers that a number of the bronchioles are left dilated after a Pfeiffer infection because of weakening of their muscular coat, and that, owing to a tendency to stagnation in such bronchioles, the natural mechanism of the lung for resisting infection is crippled.

Observations on Healthy Individuals, March, 1920.

Forty-seven venereal out-patients were examined by cultivation of swabs taken from the naso-pharynx. Four gave positive results, i. e. about 8 per cent.

This percentage of carriers of Pfeiffer's bacillus amongst the population a year after the epidemic corresponds to that of Edington, and is also within the range of such observations as exist with regard to the carrier rate in previous inter-epidemic periods. It contrasts very strikingly with the figures obtained in the epidemic period however.

Summary and Conclusions.

The general trend of the literature dealing with the frequence of infections with Pfeiffer's bacillus before, during, and after influenza epidemics is to strengthen the evidence for regarding that bacillus as the cause of influenza. We appear to be dealing with a bacillus relatively rare in the periods remote from epidemics, finding opportunity of exalting its virulence by frequent passage in numerous localized epidemics in the years immediately preceding a major epidemic, and then finally reaching that high degree of infectivity which enables it to affect a very large proportion of the community. It then rapidly increases its virulence, till at the height of the epidemic it becomes capable of producing a fulminating illness with a characteristic lesion rarely seen at other times. Young children, however, seem to stand in a different relationship from adults to infections with haemoglobinophilic bacteria, as such infections appear to be relatively frequent amongst them in non-epidemic periods. How far these haemoglobinophilic

bacteria found in the respiratory tract of young children correspond to Pfeiffer's bacillus it is difficult to say. The observations of Wollstein (47) and Scheller (10) show that differentiation within the group is by no means an easy matter. However that may be, the peculiar susceptibility of infants to infections with this class of bacteria is shown by the fact that so many of the recorded cases of influenzal meningitis have been in very young children (Ritchie (48)). And it seems not unlikely that the relatively greater susceptibility of young children to broncho-pneumonia is also related to their greater sensitiveness to infections by this group of bacteria.

Various explanations of the periodicity of influenza epidemics have been put forward. This periodicity may, of course, be due to certain cycles in the evolution of the bacteria; another explanation, however, which is frequently suggested is that an attack of the disease is followed by a long period of immunity. There are considerable difficulties in accepting the second explanation—a third is suggested by the observations of Richter (49). He showed that examination of records of disease and weather in all countries in which they had been kept over considerable periods demonstrated the coincidence of high incidence of pulmonary disease with prolonged periods of anticyclonic conditions, the atmosphere being apparently more irritating to the lungs during these periods. On this basis the periodicity is in the weather, and at more or less regular intervals the conditions recur in which the tendency to bronchial irritation is greatest. A very natural consequence of this would be that a bacterium like Pfeiffer's bacillus, which apparently tends to persist in the adult human body chiefly as an agent of chronic bronchitis, would find a special opportunity for extended propagation, i. e. for exaltation of virulence by passage.

All the above conclusions can only be tentative on account of the restricted scope of the investigations which have been made on the incidence of infections with Pfeiffer's bacillus during inter-epidemic periods, and it is emphatically required that the gaps in our information should now be made good in several respects. Amongst these are: first, that more careful and systematic investigations should be made in order to correlate clinical symptoms and bacteriological findings in acute catarrhs of the upper respiratory tract, with a view to their differentiation; second, that the percentage of carriers of the *B. influenzae* amongst the healthy population should be determined yearly in various places; third, that more data should be obtained as to the percentage of Pfeiffer's infections in various diseases of the respiratory tract, in order to find whether the high percentage of such infections recorded in pulmonary disease by one or two American investigators is usual or not.

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TABLE I. *Observations between 1900–15.*

Author.	Period and Place.	Method.	Condition of Patients examined.	Number examined.	Percentage of Infections with Pfeiffer's Bacillus.	Number of Normal Individuals examined.	Percentage of Carriers of Pfeiffer's Bacillus.
Ritchie (4)	Vienna, 1900	Cultures on plates of Pfeiffer's agar	Post-mortem observations in cases of simple or complicated bronchitis: *infants and children*	49	35 %		
Lord (quoted by Jones, Madison)(5)	Massachusetts, U.S.A., Aug., 1902–Jan., 1904 (period free from influenza epidemics)	Direct and cultural examination of sputum	Pulmonary affections amongst hospital out-patients (T.B. excepted)	186	30 % (by culture) predominant micro-organism in 25 % (as judged by direct films present in 59 %)		
Hastings and Niles (6)	U.S.A., 1903–10	Cultures on haemoglobin agar where typical bacilli seen in smears	Pulmonary affections	183	3 %–4 %		
Walb (7)	Bonn, Germany, 1903–13	No detail	Acute catarrhs of respiratory passages	—	Not found		
Jundell (8)	Stockholm, 1905–12	—	Endemic influenza; hundreds of cases every year	—	10 % amongst cases examined bacteriologically		
Wollstein (9)	U.S.A., prior to 1906	Rabbit's blood agar	Broncho-pneumonia } *in children* Measles, bronchitis, and T.B. }	— —	30 % 25 %	5 young children	Nil
Scheller (10)	Königsberg, Prussia, 1906–7, winter (influenza epidemic)	Examination of sputum	Influenza Pulmonary T.B.	— —	90 % 33 %	—	24 %
,,	1907–8, winter	,, ,,	Influenza Pulmonary T.B.	— —	20 % 10 %	—	13 %
,,	1908, summer	,, ,,	Influenza Pulmonary T.B.	— —	Nil 3·3 %	—	1½ %
,,	1908–9, winter	,, ,,	Influenza Pulmonary T.B.	—	Nil	—	Nil

Wilson and Miller (11)	England, 1908, autumn	—	Broncho-pneumonia: 5 children in one family ill simultaneously	—	Pure cultures of Pfeiffer's bacillus recovered from one case P.M.; similar infection probably missed in others
Holt (12)	U.S.A., 1909–14	Culture from sputum	Pulmonary lesions, *children*	1053	30 %–40 %
Madison (13)	U.S.A., 1910	Culture	Chronic bronchitis simulating T.B.	6 selected cases	All positive
Davis, D. J. (14)	U.S.A., some years prior to 1915	—	*Presumably mostly children*: Influenza	40	17 %
			Presumably mostly children: Broncho-pneumonia	26	39 %
			Presumably mostly children: Measles, chicken-pox, and whooping-cough	—	50 %–60 %
			Presumably mostly children: Tonsillar crypts in tonsillitis	300	1 %
Luetscher (15)	U.S.A., prior to 1915	Freshly prepared blood-agar plates	Pulmonary lesions generally	459	22 %
			Bronchitis and broncho-pneumonia only	—	50 %
Hamblett, Barnes, and Lake (16)	U.S.A., prior to 1916	Agar smeared with human blood	Pulmonary tuberculosis: closed	200	6 %
			Pulmonary tuberculosis: open	100	7 %
Wilson (17)	Belfast, several years before the 1918 epidemic	Culture from sputa on blood agar	Various	—	Infections with Pfeiffer's bacillus very rare till 1918, when they became frequent

TABLE II. *Observations between 1915 and the 1918 Epidemic.*

Author.	Period and Place.	Method.	Condition of Patients examined.	Number examined.	Percentage of Infections with Pfeiffer's Bacillus.
Hunt and Rankin (18)	Flanders, 1915	Naso-pharyngeal swab on blood agar	'Trench' fever	12	Nil
Hübschmann (19)	Leipzig, 1915 (spring)	Culture on rabbit's blood agar	P. M. observations on patients dying with marked bronchial involvement during localized influenza epidemic	110	28 % (in smears appeared to be present in 63 %)
Paltauf and Petruschky (20)	Prisoners' camps behind eastern German front, 1915	—	Bronchitis associated with typhus	—	Pfeiffer's bacillus found frequently
Arneth (21)	German troops, 1915 (spring)	Examination of sputum	Atypical pneumonias	28	58 %
Williams and Burdick (22)	Denver, U.S.A., 1915 (autumn)	—	Epidemic of 'influenza'	—	Streptococcus considered to be the cause
Scholz (23)	German troops, 1915–16	Limited bacteriological facilities	,, ,,	—	Pfeiffer's bacillus only found in cases with broncho-pneumonia
Nammack (24)	New York? 1915–16 (winter)	Exudates mixed with drop of horse blood and smeared on agar	,, ,,	50	40 % Pfeiffer's bacillus was found more frequently than any other micro-organisms and six times in pure culture
Mathers (25)	Chicago, 1915–16 (winter)	Human blood-agar plate	Severe epidemic of infections of the upper respiratory tract	61	Pfeiffer's bacillus found once
Moody and Capps (26)	U.S.A., 1916	Blood-agar plate	Investigated same epidemic as Mathers	—	6 %–7 %
Dunn, J. S. (27)	North of France, 1916–17	—	P.M. observations on cases of nephritis with pulmonary complications	—	Pfeiffer-like bacilli observed in a number of cases
Hammond, Rolland, and Shore (28)	Base, North of France, early months, 1917	Primary culture on trypsin-legumin agar, secondary cultures on blood agar	Epidemic of purulent bronchitis	20	50 % (in smears apparently 90 %)
Abrahams, Hallows, Eyre, and French (29)	Aldershot command, early months, 1917	Blood agar	As above	8	87 % (appeared in smear in all)
Robertson (30)	A. E. F., early months, 1918	Cultures from accessory sinuses of head	Various	15	Found in all

THE LAW OF CARDIAC MUSCLE WITH SPECIAL REFERENCE TO CONDUCTION IN THE MAMMALIAN HEART[1]

By THOMAS LEWIS[2]

PRESENT knowledge of conduction in the heart has come to us almost exclusively from work of the last few decades; latterly it has come more and more to mould our conceptions, not only of the normal heart-beat but of very many disorders of this beat as these are seen in sick men and women. If, by means of recent illustrations, we seek to show that medicine as a science rears itself still upon the science of physiology, no more apposite or convincing example could perhaps be found than the story of conduction in the heart, since its development from the masterly researches of Gaskell.

The Paths of Conduction.

In recent years a structure termed the *sino-auricular node* has proved to be the tissue in which the mammalian heart originates its beat (1). It is from this structure, consisting of a meshwork of small muscle-cells and nerve elements, and lying at the mouth of the superior vena cava, that the contraction process is conducted to all parts of the heart. It is not proposed again to relate the evidence for this statement (2); that the conclusion is sound is now universally recognized. This node sets the rhythm of the normally beating heart, and is under intimate nervous control.

From it the wave of the contraction process passes in all available directions; the wave as a whole spreads concentrically in the muscle of the right auricle, passing up the superior cava against the blood-stream, down the taenia terminalis to the inferior cava, from base to tip of the right appendix, and across to the left auricle and appendix through the muscle-bands which unite the two chambers. It spreads also down the septum between the two auricles, and eventually involves the whole musculature of the auricle (3). It courses through the chief muscle-bands of the auricle in their length. These bands radiate from their point of concentration in the region of the *s.-a.* node. The arrangement is eminently suited to rapid distribution of the wave. It reaches the

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[2] Working on behalf of the Medical Research Council.

[Q. J. M., July, 1921.]

specialized structures which form in the mammal the union between the auricular and ventricular portions of the heart. Here it traverses the auriculo-ventricular node; this node is composed of very small interlacing fibres which, like those of the *s.-a.* node, are richly supplied by nerves. Next it passes through the bundle and its branches; it traverses these and thus arrives simultaneously at many points of the endocardial surface of the right and left ventricles. The fibres of the bundle branches, and in some species those of the bundle itself, are the largest in the heart; they are only locally striated, and possess very large and often multiple nuclei. They are called the fibres of Purkinje. Reaching the muscle of the ventricle, the wave penetrates this everywhere along lines which radiate from the centres of the two ventricular cavities, and terminates when it reaches the pericardial surface of the heart (4). Of these conclusions also we need have no doubt; the evidence is now too overwhelmingly in their favour. It is important to realize that any studies of conduction in the mammalian heart must take strict account of these anatomical paths. Further, it must be recognized at the beginning that the propagated wave, in its course from the *s.-a.* node to the ventricular pericardium, passes through fibres of varying architecture and constitution.

In its passage from the *s.-a.* node to the pericardial surface of the ventricle, the wave of the contraction process traverses muscular tissues of four types. These may be described in terms of relative size and of glycogen content.

Size of fibre. The largest striated fibres of the heart are the Purkinje cells; next to these stand the auricular fibres; the ventricular fibres are somewhat smaller;[3] smallest of the four are the fibres of the *a.-v.* node.

Glycogen content. Glycogen is held in greatest quantity in the Purkinje cells (5); these are laden. There is a good deal of glycogen in both the auricular and ventricular muscle, and it is said by those who have compared the two (6) that the auricle holds more than the ventricle. The *a.-v.* node holds little or no glycogen (7).

Thus the fibres through which the wave is conducted vary in their structure, they vary in their chemical constitution. Now, when we find tissues which differ in structure, we may be sure that differences in function will also be discovered; further, when we realize that hand in hand with these structural differences there are parallel differences of chemical constitution, we may anticipate with some confidence differences in function which are arranged in like order.

Having considered the size and the glycogen content of the striated fibres of the heart we place these fibres in their natural order, commencing with the fibres which are largest and richest in glycogen and ending with those which are smallest and poorest in glycogen. The order is as follows:

1. Purkinje fibre.
2. Auricular fibre.
3. Ventricular fibre.
4. Nodal fibre.

[3] The last difference is not emphatic.

We will now proceed to examine and compare the power of these four tissues to conduct.

Rates of Conduction.

Many observations have been undertaken upon rates of conduction in the heart muscle; many of the methods used have been faulty or subject to very appreciable error. That has been so because the paths of conduction have been recognized only recently, and no observations upon rate of conduction can be of value which do not take into account the path followed by the wave. The statements which follow apply to the dog's heart.

In the auricle. In the mammalian auricle the natural rate of conduction is estimated with precision by first ascertaining the exact starting-point of the wave and its lines of propagation, and by subsequently measuring the times of its arrival at points on these lines. That can be, and has been, done both for the excitation wave and the contraction wave which follows it (8). The rate is the same for both processes, and approaches the average figure of 800 mm. per second. The rate of propagation may also be ascertained by stimulating the auricle rhythmically in line with two points at which the times of arrival of the propagated waves are signalled. Values similar to those obtained for the natural wave are found (9).

In the ventricle. The mammalian ventricle offers peculiar difficulties, because the rates of conduction in the ventricular muscle and in the Purkinje substance, which lines its endocardial surface, are by no means the same. The method of chief value is to propagate waves artificially from the pericardial surface of the ventricle and in line with two points at which the arrival of the resultant waves is timed. Two precautions are essential to accuracy. The muscular wall must be of considerable thickness; for this reason the left ventricle is chosen; and the point of stimulation and points signalling the waves must be close together. Otherwise the rate of conduction obtained is not that of ventricular muscle, but is a rate comprised of that of ventricular muscle and Purkinje substance. The rates of both are measurable with considerable accuracy by adopting suitable methods; that of ventricular muscle averages 400 mm. per second, that of straight Purkinje fibres is approximately 4,000 mm. per second (10).

In the a.-v. node. A direct measure of conduction in the node is not possible; that conduction is slow is suspected from the delay between the contractions of auricle and ventricle, and from analogy with the fibres of the *a.-v.* ring of the frog. An estimate of actual conduction rate in the node may be obtained by considering certain transmission intervals.

In the naturally beating heart of medium-sized dogs the transmission interval from the *s.-a.* node to the septal muscle overlying the *a.-v.* node measures approximately 0·03 to 0·04 of a second. By a different method the interval to the *a.-v.* node itself is estimated at similar figures. We may take the mean 0·035 of a second as an estimate subject to no great error (11). The interval between the

starting of the wave and the appearance of R, the chief ventricular deflexion of the electro-cardiogram, is approximately 0·10 of a second (12) (see Fig. 1). The time lost between the arrival at the *a.-v.* node and the appearance of R, therefore, is approximately 0·065 of a second. Now R begins almost simultaneously with the arrival of the wave at the apex of the right ventricle, and if we subtract the time calculated for the wave to travel along the bundle-branches to the apex of

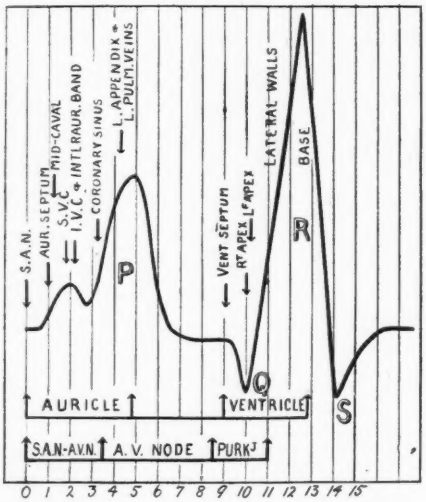

FIG. 1. An electro-cardiogram from a dog (P = auricular summit, and Q, R, and S = opening deflexions of the ventricular complex). The times at which the various parts of the muscle become active, or excited, relative to the deflexions of the electro-cardiogram are indicated above the curve on the basis of many direct observations. Below the curve, the periods during which the auricle and ventricle, each taken as a whole, become active are shown; and below this the periods during which the impulse is travelling from sino-auricular to auriculo-ventricular nodes through the *a.-v.* node and through the Purkinje system are indicated. The time lines are in hundredths of a second.

the right ventricle (on the basis of a conduction rate of 4,000 mm. per second this works out at approximately 0·01 to 0·015 of a second) we obtain a value of approximately 0·05 of a second for the passage of the node. Making an allowance for the distance traversed, let us say 10 mm. of tissue, the rate of conduction can scarcely be greater than 200 mm. per second; actually the rate is very probably somewhat less than is here stated.

To sum up, we have arrived at the following approximate figures:

Tissue.	Rate of Conduction in mm. per sec.
1. Purkinje substance	4,000
2. Auricle	800
3. Ventricle	400
4. *A.-v.* node	200

Now this is the order of the constituent fibre size, and it is the order of their

glycogen content. Our anticipation that structure and function would be found to march hand in hand is fulfilled in a remarkable manner. So striking is this example that I venture to propound the following law:

The fundamental properties of muscle will be found to vary in their degree in the four types of cardiac fibre; if for any two types we can obtain a measure, then within reasonable limits we may predict the degree for the remaining two types by placing all four in their natural order.

This law is propounded in the belief that it will lead us, if used circumspectly, to a closer understanding of many phenomena exhibited by the mammalian heart. In the mammalian heart the structures which possess the rhythmic property in highest degree are the *s.-a.*[4] and *a.-v.* nodes; they are alike constituted of fine muscle-fibres. The relative rhythmicity of the auricular and ventricular muscle and of the Purkinje fibres is not known; but it is known that all possess the function in lower degree than the nodes.

The law as I have stated it would lead us to anticipate that Purkinje fibres are the least rhythmic.

The phenomenon of 2:1 *response (half response).* We may now examine a curious but perfectly understood phenomenon, namely that of 2:1 response in cardiac muscle responding to extreme rates of stimulation. If the muscle of the mammalian auricle is stimulated at increasing rates, there comes a time when it will no longer respond to each stimulus. When this rate is reached, the auricle begins to respond to alternate impulses only. This condition of 2:1 response is due to the responsive phase of the cycle being brought to the vanishing point as diastole is reduced; alternate impulses fall on muscle which is still in the refractory state, which is still inexcitable; the critical rate at which this 2:1 response occurs may be taken as an index of the refractory period in heart muscle. Now the refractory period of auricular muscle is of shorter duration than is that of ventricular muscle, for its systole is shorter. Applying the law of cardiac muscle, we may predict that the duration of the refractory state in the muscle of the *a.-v.* node is longer than in either auricle or in ventricle. Recently this prediction has been put to the direct test, and it is found that the law holds good; the critical rate at which half response occurs in the auricular muscle is approximately 450 per minute; the critical rate for the *a.-v.* node lies with great regularity between 270 and 300 per minute; the critical rate for the ventricle is intermediate. Drive the auricle at rates surpassing 300 per minute and the ventricle will beat at a lower rate; but it is not the ventricle which fails to respond, for the ventricle will respond to each stimulus if these are directly applied to it; it is the *a.-v.* node which fails to transmit.[5] The *a.-v.* node is a natural blocking-point (13); it is a natural blocking-point because the length

[4] According to the law this node should be deficient in conducting power; very possibly the condition known as 'sino-auricular' block is due to retarded or inhibited escape of the wave from this node to the surrounding auricular tissue.

[5] Recent and unpublished observations with Dr. A. N. Drury and Dr. C. C. Iliescu.

of its refractory period is high.[6] This conclusion is cited to illustrate how the law of cardiac muscle may be used; in the first instance it was foretold that the critical rate for the *a.-v.* node would prove the lowest; it has been put to actual test and proves to be the lowest.

The law of cardiac muscle may be exemplified more fully in the accompanying table, in which the structure and constitution of the fibres are correlated with the more important properties of cardiac muscle. The order expressed in each vertical column is the order of decline in the characters or properties which are indicated in the head-lines of these columns. For the most part the order is based on actual observation; the bracketed figures are, however, theoretical; these are in the nature of predictions.

In as far as the predicted order is found in the future to obey the law, in so far will the view be confirmed that, on the one hand, the functions of the Purkinje fibres in general approach towards those displayed by nerve, while, on the other hand, the functions of nodal muscle approach towards those displayed by involuntary muscle. The last conception reminds us of the intimate control of involuntary muscle by the plexuses of Auerbach and Meissner; the intimate nervous control of the nodes of the heart may yet prove to be ordered upon a plan morphologically similar.

The Law of Cardiac Muscle.

	Order of Decline.						
Fibre.	Size.	Glycogen Content.	Conducting Power.	Absolute Ref. Per.	Rate of Recovery of Excitability.	Rhythmicity.	Contractile Power.
Purkinje	1	1	1	[4]	[1]	[4]	[4]
Auricular	2	2	2	3	[2]	[3]	[3]
Ventricular	3	3	3	2	[3]	2	[2]
Nodal	4	4	4	1	[4]	1	[1]

The order denoted by bracketed figures is at present purely theoretical.

Altered Conduction.

Although we may, for convenience, separately name several of the properties of cardiac muscle, it is not yet proven that these properties are independent functions in the sense which Engelmann would have led us believe. One of the seemingly most convincing cases which Engelmann made out was for the independence of the functions excitability and contractility (14). Recent observations (15) rob his chief evidence of its weight; the general trend of conclusion is opposed to the conclusion which he sought to establish. Engelmann was equally convinced of the independence of excitability and conductivity, though his argument for this conclusion was of a more speculative kind (16). This problem of the interdepen-

[6] To this is probably due the failure of interpolated extra-systoles of the ventricle to reach the auricle, a phenomenon which has hitherto remained mysterious.

dence or independence of excitability and conductivity has long been contended in the case of nerve; the compass has swung from one pole to the other. Similarly, in the case of muscle, opinion has swung to and fro; the case for interdependence has been emphasized of recent years by Straub (17) and Tait (18). Recent observations strongly support the last view. We may now summarize them, but, before doing so, it is to be pointed out briefly that nearly all the studies which concern themselves with altered conduction in the heart deal not with normal changes in the muscle but with changes which are essentially of a pathological kind. Of changed conduction in the heart beating under wholly natural conditions we have little exact knowledge;[7] such knowledge as we possess goes to show that conduction is relatively a very stable property, and that if changes in the rate of conduction do occur in the intact and healthy body such changes are uncommon or of very minor degree. This contention is one of some importance, for we are apt to forget that the conditions which we impose upon muscle experimentally, such as change of temperature, of pressure, of innervation, or of nutrition, conditions which provoke obvious defect in the conducting power of the muscle, are unnatural. Speaking of lowered conduction, to the neglect of possible minor changes, we may say that when conduction is altered by the means named the fibres of the muscle which is under observation are already verging on death. Thus, while we may be in a position to speak of conduction as a property of cardiac muscle, as yet we are scarcely warranted in regarding altered conduction as physiological.[8] Physiologically, as has been stated, conduction is stable; if conduction may be spoken of as a function of cardiac muscle, depressed conduction may not as yet be regarded as a normal event.

Having stated the belief that altered conduction, in so far as anything but very minor changes are concerned, is essentially pathological, that it is essentially a condition leading up to extinction of functions as a whole, the reasons may be stated for believing that the changes as we see them might reasonably be interpreted in terms of altered excitability.

Heart-block as a result of raised rate. The subject may be introduced by considering the reaction of the muscle to excessive rates of stimulation. If the muscle of the mammalian auricle is driven at rates which much surpass those occurring under natural conditions the speed at which the excitation wave is transmitted falls conspicuously. It falls progressively as the rate is advanced beyond a certain point. If the rate is advanced farther the phenomenon of 2 : 1 response is witnessed. We have recently obtained what appears to be convincing evidence[9] that the reduced rate of conduction from point to point and the 2 : 1 response, both of which occur as the rate of stimulation is advanced, are attributable to one and the same underlying cause. The very fact that the

[7] The most striking instance of physiological block has been found in hibernating bats by Miss Buchanan (*Proc. Physiol. Soc.*, 1911, xlii. 21).

[8] With perhaps the single exception named.

[9] The detailed evidence for the statements which follow is given by Lewis, Drury, and Bulger, *Heart*, Lond., 1921, viii.

last is always foreshadowed by the first as the rate rises at once suggests this relation. There is evidence that as the rate rises the fibres do not assume this halved rhythm simultaneously, but that one fibre after another is affected. When all[10] are affected 2 : 1 response of the muscle as a whole is seen ; when a proportion is affected the stimuli enter and travel through muscle, some fibres of which are in the responsive and some are in the refractory state. It is this *partially refractory* state of the muscle, as a whole, which is responsible for the increased delay in the waves' transmission from point to point. When a wave is transmitted through cardiac muscle, the course which it takes is not precisely a straight line ; the wave is travelling in a syncytial system of fibres, and these fibres are grouped in bands which are often waved or even interlacing. In following the shortest path which it can take, its track is consequently in

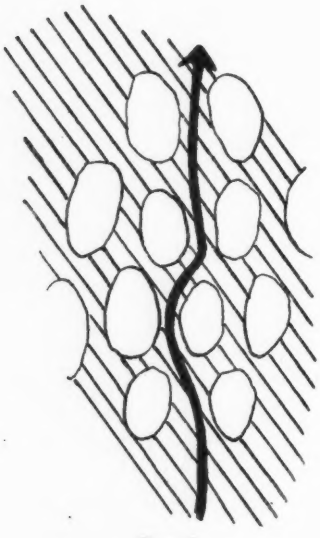

FIG. 2.

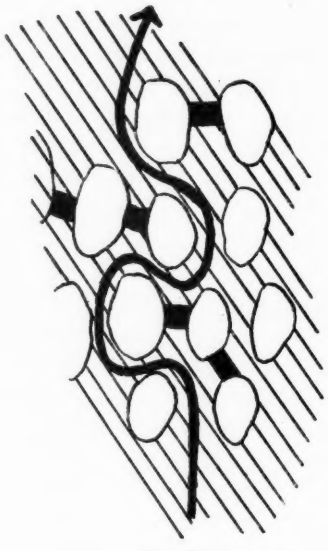

FIG. 3.

a measure sinuous (Fig. 2). Now suppose that the wave in its course through the responsive fibres encounters numerous fibres which are refractory ; its natural path is obstructed and the wave turns from side to side, may even turn back, before it finds a free channel of advance (Fig. 3). Briefly, the normal sinuosity of the path will increase in its degree ; the way will be longer, and the transmission rate from point to point will be reduced. We possess what we regard as proof that reduced speed of transmission, in response to unnaturally high rates of stimulation, is brought about in this way. It is known that the halved rhythm is due to alternate impulses falling upon muscle in which all the fibres are refractory ; we explain the reduced conduction rate which foreshadows it by supposing that the impulses enter muscle in which a proportion of the fibres are refractory.

[10] Or a sufficient number.

If our explanation is a correct one, then any influence which reduces the length of the refractory period should restore the rate of conduction to its original level; just as it should abolish the condition of 2:1 response. The most potent method of reducing the refractory period of auricular muscle is by vagus stimulation; this stimulation shortens systole, and with this shortening the refractory period falls. Vagus stimulation has precisely the effects anticipated. It abolishes the 2:1 response, it restores the rate of conduction to its natural level. Now this example is the more notable because we might have been led to suppose that vagal stimulation would reduce the rate of conduction, and because vagal stimulation is known to raise the threshold of excitability. Actually, the vagus has not the first effect; in the auricle it does not affect the rate of fibre conduction; this factor, therefore, need not be discussed. The raising of the threshold of excitability would act, if it acted at all, in a direction contrary to that which is observed. There can be no doubt, therefore, as to the meaning of the reaction, and no doubt as to the nature of the disturbed conduction. When the rate of auricular stimulation is advanced, then comes first a prolongation of the transmission intervals; then comes finally a failure of response, which is at first occasional, but which is eventually a 2:1 response. All these disturbances arise from the impulse entering, or the wave progressing through, muscle in which some or all of the fibres are refractory. Broadly speaking, the changes seen in an auricle which responds to high rates of stimulation are identical with those which characterize heart-block as this occurs at the *a.-v.* ring. That failure to respond may result from the relation of alternate impulses to the refractory period has been long recognized, but what has not been recognized hitherto, but has now been demonstrated, is that *prolongation of the transmission intervals* may arise in similar manner. This clear demonstration upon the muscle of the auricle obviously calls us to revise our ideas of heart-block as it is witnessed between the auricle and ventricle.

It has been stated already that 2:1 block is produced at the *a.-v.* ring by rapid stimulation of the auricle, and this block has been ascribed to similar causes, namely, to alternate impulses falling during the refractory period of the nodal muscle. This 2:1 response is foreshadowed, just as is the 2:1 response of the auricle itself, by prolonged transmission intervals. It can scarcely be doubted that they are attributable to a state of partial refractoriness, just as are the comparable prolongations in the auricular wall. But there is a serious difficulty; this form of heart-block at the node is not abolished by vagal stimulation, it is enhanced by it. The vagus is incapable of influencing fibre-conduction in the auricle, although it is known to exert a powerful control over this muscle. This being proved, an action of the vagus upon fibre-conduction in the node cannot be admitted, unless we are prepared to suppose that the vagus controls the properties of this node in a fashion fundamentally different from its control of auricular muscle. It is obviously impossible to assume that in comparable conditions disturbed transmission is due to one cause in the auricle and to a fundamentally distinct cause in the node. It would be most difficult to assume

that the vagus controls a hypothetical and independent property 'conduction' at the node, and fails to control it in the auricle. Although the vagus does not influence fibre-conduction in the auricle, it does produce prolonged transmission intervals and block in the auricular wall; *it abolishes both.* There is, therefore, in point of fact, a sharp contrast between the effects of vagal stimulation in the auricle and at the *a.-v.* junction, when it plays upon disorders of transmission invoked in these comparable ways. This contrast requires explanation, and the

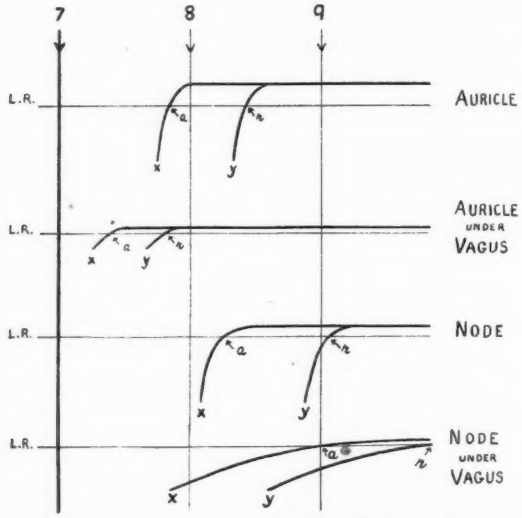

FIG. 4. A diagram illustrating the recovery of excitability on the basis of the hypothesis discussed in the text. The auricle is being stimulated by rapid rhythmic shocks, represented by the lines 7, 8, and 9. The muscle of the auricle responds to shock 7, and after its systole is complete its excitability recovers; the rate of recovery is rapid, but owing to the high rate of stimulation the fibres do not begin to recover simultaneously. Fibre *x* becomes responsive at *a*; this point marks the end of the absolute refractory period. Fibre *y* becomes responsive at *r*; this point represents the beginning of the wholly responsive stage. Period *a–r* represents the stage of partial refractoriness, and during this stimulus 8 falls on the muscle.

In the second line the auricle is under vagal stimulation. Although excitability recovers more slowly, yet, owing to recovery starting earlier, the wholly responsive stage is reached before stimulus 8 comes. Conduction in the auricle is therefore improved.

In the third line the nodal muscle is represented. The absolutely refractory period is long, and stimulus 8 falls within it; stimulus 9 falls in the phase of partial refractoriness. In these circumstances the node would respond to alternate stimuli.

In the fourth line the node is represented under vagal stimulation. It is supposed that while the absolutely refractory period is a little shortened, the rate at which excitability recovers is much reduced; consequently conduction is further depressed. The 9th stimulus is represented as falling just in the period of absolute refractoriness. L. R. = level of excitability necessary to yield response.

law of cardiac muscle brings us, so it is believed, to an understanding of the difference and enables us to adopt an explanation which, though it is still hypothetical, avoids the serious difficulties of the alternative explanations discussed. According to the law, the same properties of cardiac muscle are held by the different tissues in different degrees; we may assume with some measure of confidence that a given property will be affected differently by nerve control according to the order of

tissue upon which the nerve acts. According to our law, and according to observations first suggested by this law, the refractory period in the node is longer than in the auricle. We may not assume that the vagus fails to influence the duration of the node's refractory period, but may we not assume that vagal stimulation, while it is known profoundly to influence the length of the refractory phase in the auricle, has not a proportionate effect upon its length in the node? That would help us to explain why the vagus will abolish defects of transmission arising out of the refractory period in the auricle, while it fails to abolish similar defects in the node. But under this assumption the reason why the block is much increased at the node, and is not increased in the auricle, would still remain not clear.

We conclude in the first instance that the block originally produced by excessive rate is in both regions conditioned by unrecovered excitability, and that failure to recover is caused by lack of sufficient time to recover. By stimulating the vagus and thus profoundly reducing the length of systole in the auricle, a sufficient time for recovery is allowed. But clearly the degree to which excitability recovers is influenced not only by the time factor, it is influenced also by *rate* of recovery. If this rate of recovery is slower in the case of the node than in the case of the auricle—and we are led to expect that this is so in that there are clear indications that the metabolic processes in the node are the slower—may we not assume that where it is already slow, it will be more effectively retarded by the vagus influence? Let these assumptions be granted, and we develop a hypothesis which, while concerning itself with excitability only, offers an adequate explanation of the phenomena witnessed in both regions. For whereas the major influence of the vagus will be exerted towards increasing the period of recovery (by shortening systole) in the case of the auricle, thus rendering it more excitable when the next impulse reaches it, in the case of the node the major influence will be exerted to delay the rate of recovery, thereby rendering it less excitable when the next impulse reaches it. Thus the end results would be opposed. We suppose the two influences, opposed as they are, to be manifested both in the auricle and in the node, but that in the case of the auricle the lengthened time of recovery overshadows the reduced rate of recovery, while in the case of the node the converse holds.[11]

If the vagus has the twofold influence suggested, then it would be anticipated that the effect, which is in general the minor one, and consequently overshadowed, might in special circumstances become distinct. This appears to be the case, for several curious, and at first sight discrepant, observations are on record. Thus in certain of Erlanger and Hirschfelder's experiments heart-block produced in the *a.-v. bundle* by compression was not increased by vagal stimulation, but seems

[11] When vagus stimulation produces prolonged transmission intervals from auricle to ventricle, rather than dropped beats, it is supposed that it does so because the excitability recovers to the level at which response is possible at different time instants in different fibres; and that, as in the case of prolonged intervals in the auricle, the result is sinuous movement and increase in the length of the path travelled.

actually to have been relieved (19). There are also Gaskell's observations upon his auricular bridge in the cold-blooded heart (20); in these experiments vagal stimulation sometimes, but by no means always, produced block.

Heart-block by compression. This well-known method of producing prolonged transmission intervals and failure of response is comparable with many instances of block produced by disease. Often such block is not to be described in terms of muscle property, but in terms of tissue destruction. The lesser grades of block are sufficiently explained by surmising a general depression of functional efficiency. To particularize, such block might be attributed in some instances to a decline in the rate at which excitability recovers; in others it is conceivable that increased tension, by invoking a more isometric form of contraction, prolongs the systolic period and so shortens the time allowed for recovery.

Heart-block arising from poisons. These varieties of heart-block are, perhaps, amongst the most interesting exhibited by the heart. The poisons which are known to produce altered conduction are now almost innumerable; a very large proportion of all poisons which act powerfully on the muscle will, in sufficient doses or in given circumstances, produce block. A few of the more conspicuous of these may be cited, namely, the products of asphyxia, the whole of the digitalis series, potassium chloride, aconitin, and all drugs exerting a powerfully stimulant effect on the vagus, such as pilocarpine and muscarine. All these drugs, when given in doses sufficient to produce block, bring the muscle near, if not actually, to death. All are known or suspected to raise the threshold of excitability; some are definitely known to reduce the period of recovery by prolonging systole; heart-block produced by each may be explained by changed excitability; the action being upon the refractory period or upon the rate of recovery. There is another series of poisons, of which atropin may be taken as a striking example, which, having only an exalting influence upon the heart's metabolism, may nevertheless hinder conduction. The relation of atropin to block is a curious one. Atropin hinders conduction in the auricle only when the auricle is responding to high rates of stimulation; that is so because it prolongs the refractory period. It has no effect on the rate of fibre conduction (21). The relation between manifested block and the rate at which the heart is beating is one which has suffered an unfortunate neglect. Enough has been said to make it clear that, although there is much for us yet to learn, our conception of these protoplasmic poisons tends to move in one direction, namely, to couple apparent defects of conduction with defects of excitability; in what measure these defects are to be attributed to delay in the starting of this property towards recovery (lengthened systolic period), and to what extent they are to be attributed to delay in the rate of recovery once this has begun, is for the future to decide in the instance of very many of the poisons named. Now much of what has been said in regard to poisons is frankly speculative; their action has been discussed chiefly with a view to pointing out that their effects may be explained without introducing conduction as an independent property.

To sum up, there is probably no example of altered transmission of which

we have sufficient knowledge to speak, whether such is produced by nerve influences, by temperature change, by pressure or poison, which may not be explained on the basis of depressed function as a whole ; [12] if we are asked to speak particularly in terms of the properties of cardiac muscle, then it is in terms of *excitability* that these changes are first to be interpreted. In so speaking, we must ever bear in mind the morphology of the tissues in which the defect is exhibited, remembering that the four types of tissue display their several properties in different degrees, according to the law of cardiac muscle which has been formulated.

[12] In the case of atropin the depression is confined to the period of diastolic rest, and only occurs at high rates of beating.

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STUDIES IN THE METABOLISM OF RICKETS[1]

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I. IS RICKETS DUE TO A DEFICIENT SUPPLY OF CALCIUM TO THE BONES?

The Calcium Content of the Blood, Muscle, and Brain, in Experimental Rickets in Dogs.

An historical sketch of the more important investigations already recorded upon rickets prepared by one of us (L. F.) was published as an introduction to Miss Ferguson's Report to the Medical Research Committee, 'A Study of Social and Economic Factors in the Causation of Rickets', Special Report Series No. 20, 1918.

It is unnecessary to recapitulate this. It showed clearly that the etiology of the disease is no better understood now than when Glisson described it in the seventeenth century, in spite of all the work that has been accomplished since then.

As Albu and Neuberg (1) say, after a full consideration of the calcium metabolism in rickets and of the various theories which have been advanced as regards the nature of the disease, 'Die Geschichte der Rachitis ist . . . . . mit einer Fülle neuer Hypothesen aber wenigen Tatsachen bereichert worden'.

That rickets is not simply an impaired calcification of bone or an exaggerated decalcification, as so many consider it to be, is shown by its clinical features and by the nature of the pathological changes in the bones. The general malaise of the child, the profuse sweating, the intense muscular weakness and the tendency to the development of tetany, all indicate some general disturbance of which the bone changes are merely one manifestation, and any explanation of the nature of the disease must explain this group of symptoms.

Further, the pathology of the bone changes and the formation of the characteristic osteoid tissue mark it as a disease *sui generis*, totally different from conditions of a mere failure in calcification.

Since one of the most patent changes is the softening of the bones, great

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[2] Throughout this and the next part Noël Paton and Leonard Findlay are responsible for the general plan of the work, Noël Paton for the experimental and Leonard Findlay for the clinical part. J. Sharpe is responsible for the chemical analyses.

interest has, for long, centred round the behaviour of lime salts in the etiology of the disease. It is possible that in considering the relationship of calcium to bone development its significance as an essential constituent of all the tissues and its importance in maintaining and controlling their activities may have been forgotten. A due proportion of calcium ions is essential alike for muscular activity and for the control of the nervous system, and the store of calcium in bone is well known to act as a source of supply when this is cut off from without, as in starvation. Changes in the amount of lime salts in bone may thus have a significance altogether outside the skeleton.

Broadly speaking, the diminished amount of calcium in the bones must be due to one, or all, of three causes:

1. A deficient supply of calcium to the bones, due to either
   (*a*) A deficient supply of calcium in the food.
   (*b*) A deficient absorption of calcium from the food.
2. The inability of the growing bone to fix the calcium brought to it, or,
3. A non-retention of calcium by the rachitic bone, i. e. decalcification.

Normal ossification involves the two processes of the deposition of lime salts (calcification) and the re-absorption and removal of these (decalcification), as the growth extends outwards, and as the spongy cancellous tissue of bone is produced. The salts removed in the process of re-absorption are available to be used again in the calcification as it spreads outwards.

Under normal conditions these two processes are perfectly co-ordinated. If this co-ordination were upset in the direction of failure of the growing part of the bone to use the lime from the normally decalcifying part, the same result on the metabolism of the lime would be produced as would be caused by a simple exaggeration of decalcification.

Deficient supply of calcium was formerly very generally considered as the cause of the bone changes, but the experimental work recorded seems to negative this possibility.

One of the first workers was Roloff (2), who made investigations upon the nature and cause of a condition called 'Knochenbrüchigkeit', which occurred in endemic fashion among cattle, sheep, and swine, and which was occasionally observed also in horses and goats. Clinically it was said to resemble, according to the age of the animal, rickets or osteomalacia. The animal became lame, disinclined for exercise, seemed to suffer pain, and curvature and fracture of the bones resulted. It was more apt to occur during the winter months, both in young and in old animals, and less frequently in animals performing work than in those housed all day long in stables. Pathologically, it was characterized by softening of the bones, with a decrease in the calcium content, great thinning of the bony trabeculae, increase of the marrow, widening of the epiphyseal line, and the formation of what was called by him 'osteoid' tissue. By 'osteoid tissue' he meant a transition from bone to marrow on the inner aspects of the trabeculae, and he stated that it is simply what is found normally, but occurring at the

wrong stage when the lamellae are fully formed and have ceased to increase at the periphery. He looks upon it as a definite decalcification, and he does not seem to associate it with any change of the epiphyseal lines. Roloff (2) concluded that the condition was due to a deficient amount of calcium in the diet. Most of his paper, however, is devoted to a theoretical discussion with numerous chemical analyses of the different food stuffs and his arguments are anything but convincing. Although he mentions the disease as occurring in certain farms where the stock was well fed, and absent in other farms where the animals were poorly fed; and although he gives analyses of the milk of two sets of sheep, one with affected and the other with non-affected lambs, in which the milk consumed by the former was richer in fats, protein, and salts than that consumed by the latter, he adheres to his opinion and explains away these disturbing facts by merely stating that animals do not all take the same amount of any one food, nor equal amounts of different elements in a mixed diet, so that *in all probability* the affected animals had consumed less of the calcium-rich food stuffs! The increased demand for calcium during pregnancy and lactation he considers the reason for the condition occurring more frequently in pregnant and suckling animals.

Weiske (3) shortly afterwards unsuccessfully attempted to induce a similar condition experimentally by feeding an adult goat and growing lambs on a calcium-poor diet. The animals died, but their bones were not deficient in calcium. Examination of Weiske's diets shows that they were insufficient in the essential proximate principles. The animals seem to have died simply from inanition.

E. Voit (4) experimented upon growing dogs. In his first experiment a young dog was fed upon a calcium-poor diet and developed symptoms resembling those of rickets. In his next experiment three pups of a litter were taken, and one was killed to serve as a check. The other two were fed, the one upon a calcium-poor diet of lean horse flesh with bacon (*Speck*), and the other upon the same diet with the addition of bone ash. The first developed the symptoms of rickets, lost its appetite, and finally suffered from diarrhoea with bloody stools. Both were killed on the 29th day of the experiment.

Voit states that the bones were soft, the epiphyseal lines more than twice as wide as normal, definitely irregular, and that the change from cartilage to bone was also irregular, and not sudden as occurs in normally growing bone. The chief change between the bones in the normal and the diseased animals was the irregular arrangement of the cartilage cells preparatory to the deposition of calcium.

Undoubtedly this description suggests the rachitic picture, but from his estimation of width of the epiphyseal line, this would seem to be much less marked than is usually met with in experimental rickets. Further, there is an absence of any mention of a definite delay either of calcification or of ossification.

The amount of calcium was markedly reduced, not only in the bones, but also in the muscles, blood, and other organs. He confesses, however, that he

obtained more calcium from the body than could be accounted for in the food, a finding which makes it somewhat difficult to estimate the value of the results.

As Stoeltzner (5) rightly says, 'the epoch-making work of Pommer (6) on rickets in 1885 gave a new conception of the disease'. It was he who first described the essential characteristics of rachitic bone. The chief features of rickets are, according to him, the formation of osteoid tissue, the increased and irregular formation of cartilage, the delay in calcification, and the delay in ossification, the trabeculae being composed in great part of a non-calcified osteoid tissue. Conclusions based upon work published prior to that of Pommer must be accepted with caution. Weiske chiefly depended on chemical analysis, and Roloff and Voit's histological descriptions are not sufficiently detailed.

Stoeltzner reinvestigated the question in conjunction with Miwa (7) in 1898. These authors fed a growing dog of large race on a diet of flesh and distilled water, and got the clinical and naked eye pathological features of rickets. Histological examination, which was carried out in great detail, revealed, however, no true rachitic changes but simply osteoporosis. The bones were soft, the marrow abundant, the epiphyseal lines slightly thickened, but there was neither irregularity in calcification nor delay in ossification, and any bone that was laid down was fully formed.

Oehme (8) still later experimented on growing dogs with a calcium-poor diet, and found a condition of osteoporosis apparently due to the absorption of the already calcified bone to supply the calcium for the growing part. By the administration of strontium phosphate to these dogs a condition resembling rickets was produced.

Dibbelt (9) (1910) has also studied the influence of a calcium-poor diet in pregnant animals and their suckling young, and states that he has found that the tissues, but chiefly the bones, part with calcium in order to supply the needs of the foetus and young animals. The bones of the foetus remain normal, while those of the mother undergo a marked change which Dibbelt calls osteomalacia. Since the milk of animals fed on a calcium-poor diet contains less calcium, changes in the bones of the young arise. These changes are characterized by a hypoplasia of the osseous tissue, and the production of osteoid tissue, in his opinion not identical with true rickets. In this conclusion he is supported by the work of Carl Rose (10). Dibbelt remarks that these changes were as marked as those found in experiments with confined animals by Findlay (11) but the changes in Dibbelt's cases, according to his published illustrations, are nothing like so marked, either to the naked eye, or histologically, as those in Findlay's animals, which showed great widening and irregularity of the epiphyseal lines, delay in calcification and ossification and the formation of osteoid tissue, features which do not appear in Dibbelt's figures. Schmorl, who examined Findlay's specimens, pronounced the changes identical with those which occur in human rickets.

Stoeltzner (12) from an examination of all the evidence definitely rejects the view that rickets is due to a decreased supply of calcium, and, from a consideration

of the experimental work upon the influence of strontium on bone formation, concludes that the essential change in rickets is an inability of the ossifying tissue to fix calcium. He further emphasizes the fact that calcium, like strontium and phosphorus, stimulates the formation of ossific uncalcified tissue, but that, while strontium is not fixed to any great extent and leads to soft bone, calcium normally is fixed and leads to the production of hard bone.

That a deficiency in the supply of calcium is not the causal factor in rickets is further indicated by the results recorded by Watson and Noël Paton (13) on the development of rickets in young dogs. In all the pups the calcium intake was ample, and it was as great in those on separated milk as in those on whole milk. Further, it was smaller in those in the bread experiments which escaped rickets than in those on oatmeal experiments which developed it.

These observations seem to show that a calcium-poor diet produces an osteoporosis with changes in the bones which somewhat resemble, to the naked eye, those seen in rickets, but which lack the characteristic histological features.

In the next paper metabolic studies are recorded which seem to show that rickets is not due to diminished absorption of calcium from the alimentary canal.

If rickets were due to a failure in the supply of calcium, either from deficiency in the food or from imperfect absorption, a marked decrease in the lime of the blood and tissues, other than bone, should be manifest, especially as the work of Aron (14) has shown that in young dogs on a diet insufficient to allow of proper growth, the skeleton increases to a much greater extent than the other tissues, while the proper proportion of its inorganic constituents is maintained.

The Calcium Content of the Tissue and Blood.

1. *Calcium of the tissues.* Stoeltzner (5) examined the calcium content of the tissues in three rachitic children and found that the tissues other than the bones were richer in calcium than the tissues of healthy children. Brubacher (15) obtained similar results. He based his conclusions on the analyses of three non-rachitic and six rachitic children. One of the former was a premature child of twenty-eight weeks, another a dead-born of thirty-six weeks, and the remaining child was four years old. Of the six rachitic children examined, one was an example of so-called congenital rickets (? congenital syphilis) and was one month premature; one of the children was one year old, one was one year and seven months, one three years and ten months, one twelve years and eight months, and the remaining child was supposed to be under one year. He does not state the stages of the disease when the examinations were made, but since in all of them the bones contained much less ash than normally, it may perhaps be concluded that the cases were examples of active or at least unhealed rickets. The normal and rachitic material of such a series is, nevertheless, hardly comparable, and Brubacher's results cannot therefore be accepted as conclusive.

Aschenheim and Kaumheimer (16) found the calcium of the muscles of rachitic children markedly reduced. In their six cases the calcium varied from

0·0255 to 0·057 per cent. in the fat-free dried substance, against 0·065 to 0·0817 given as the normal.

2. *Calcium of the blood.* As regards the calcium of the blood many observations have been recorded with the most diverse results. This is probably because different methods of analysis have been used by different workers. Katzenellenbogen (17), using Wright's method, found no difference in the calcium content of the blood at different ages except that in the newly born it was relatively low. He found no difference between the amount of calcium in naturally and in artificially fed children. On a calcium-poor diet the percentage in the blood was decreased. In rickets the amount was found to be normal, but in spasmophilia rather decreased.

Aschenheim (18) found in adults and children 8 to 10 mg. calcium per 100 c.c. of blood. In rickets it was generally lower but in some severe cases actually higher. In osteomalacia it was very high.

Howland and Marriott (19) made a series of observations on the calcium content of the blood serum. They state that in almost all instances, irrespective of age, and always in infants, the calcium content was above 10 mg. and seldom more than 11 mg. In two of their seven adult cases, however, estimations of 9·2 and 9·8 are recorded. In uncomplicated rickets they say that no deviation from the normal was observed, yet their average figure for rachitic cases was 9·4 mg., and one estimation of 7·9 mg. is recorded which is distinctly below the lowest for normal infants. They estimated the calcium by a colorimetric method depending upon the decolourization of ferric thiocyanate by oxalate, a method which they admit 'requires a considerable experience in the various manipulations and in the final readings'.

Denis and Talbot (20) have recently published a paper on the calcium in the plasma of the blood of children suffering from a wide variety of diseases. They used a modification of Lyman's (21) nephelometric method and got results varying from 1·00 to 13·5 mg. per 100 c.c. plasma! The average result of all their 119 examinations was 6 to 8 mg. In the active stage of rickets readings varying from 2·0 to 8·0 were obtained, but in all the severe cases the disease was complicated by other conditions. In twenty-one cases convalescent from rickets, but also complicated with other diseases, they found variations from 4·5 to 11·2 mg. They remark that 'While in some of these cases the calcium values are distinctly below normal, the interpretation of the results is seriously complicated by the fact that several of the patients who gave low calcium values were also suffering from other maladies, (pneumonia predominating) which might also affect the calcium level in the blood. No conclusions can, therefore, be drawn from these figures.'

Lyman's method has been severely criticized by Kramer and Howland (22) on the ground of the variable results obtained in different normal individuals.

All these investigators used serum, assuming that the calcium of the blood is present in the plasma alone. They had apparently accepted the results of Abderhalden, obtained in the horse, as valid for man, although the older analyses

of Schmidt and the results recorded by Rona and Takahashi (23) seem to point to a certain proportion of the calcium being present in the blood-corpuscles. The more recent work of Cowie and Calhoun (24) gives the following results:

	Mg. Ca per 100 c.c.	
	Ox.	Man.
Whole blood	7·82	8·45
Serum	8·67	12·07
Washed corpuscles from defibrinated blood	2·07	3·47
Unwashed „ „ „ „	4·98	4·26

The results of three observations made by us confirm their findings. (For method, see below.)

	Ca in Mg. per 100 c.c.		
Age.	Whole Blood.	Serum.	Corpuscles (calculated).
7 years	9·0	14·0	3·0
17 „	7·8	12·7	1·5
27 „	7·8	12·7	1·5

Taking the plasma as 56 per cent. and the corpuscles as 44 per cent. of the blood, this gives in 100 c.c.'s of whole blood the proportion of calcium in serum and corpuscles in mgs.—

	1	2	3
Serum	7·64	7·1	7·1
Corpuscles	1·36	0·7	0·7
Percentage in corpuscles	15	9	9

It is therefore manifest that calcium determinations should be made upon the whole blood, in spite of the trouble caused by the presence of iron in the corpuscles.

Present Investigations.

A. *Method of Analysis.*

The same method was employed all through the work for determining the calcium content of food, faeces, brain, and blood.

A known weighed amount, or in the case of blood and milk, a measured volume, of the material was dried and then ignited in a silica basin until all or most of the carbon was driven off, care being taken not to employ too great or prolonged heating. The residue was dissolved in hydrochloric acid and a little water, filtered and well washed. Any free carbon left after the treatment with hydrochloric acid was then further ignited and again treated with hydrochloric acid and water, and added to the first filtrate. To the filtrate excess of ammonium hydrate was added and then an excess of acetic acid. The calcium was thus brought into solution, and any precipitate of phosphate of iron was filtered off and well washed with hot water. Oxalic acid was added to the filtrate, precipitating the calcium as oxalate. The determination was finished in the usual way by dissolving in sulphuric acid and titrating with N/10 potassium permanganate.

B. *Results.*

1. *The Calcium Content of Muscle and Brain.* The following determinations of the calcium content of muscle and brain were made in the two litters of pups used for the observations recorded in the *British Medical Journal* (25).

Table showing Calcium Content of Muscle and Brain in Rachitic and Normal Pups in mg. per 100 grm.

Designation of Animals.	Muscle.				Brain.			
	Controls.		Rachitic.		Controls.		Rachitic.	
		Average for Litter.		Average for Litter.		Average for Litter.		Average for Litter.
Litter 1	0·013		0·010		0·010		0·013	
	0·010	0·011	0·016	0·014	0·017	0·013	0·012	0·012
			0·016				0·011	
Litter 2	0·015		0·014		0·015		0·016	
	0·017	0·015	0·012		0·013	0·013	0·011	
	0·014		0·015	0·014	0·013		0·015	0·013
			0·013				0·012	
			0·015				0·013	
Average of all animals	0·014		0·0138		0·013		0·0127	

From the above table it is seen that, if all the controls are grouped and all the rachitic pups are put in a separate group, the average calcium content of both brain and muscle is exactly the same as in health. If, however, each litter is taken separately it is seen that in one litter the rachitic muscle is richer in calcium than that of the healthy animal, whereas the brains of the controls are slightly richer in calcium than the brains of the rachitic animals. In the other litter the calcium content of both normal and rachitic brain is alike, but the muscle in the case of the controls is slightly richer in lime. There is, however, very little difference between the healthy and diseased animals, and when the individual figures are examined the range of variation and overlap are seen to be so great that it must be concluded that neither brain nor muscle show any deviation from the normal.

2. *The Calcium Content of the Blood.* (a) *At Different Ages.*

As already indicated, Howland and Marriott, from their observations upon human serum by a colorimetric method, concluded that the calcium content of the blood is uninfluenced by age, thus confirming the conclusions of Proskauer (26). Neurath (27), however, found the calcium content highest at birth, sinking later to a lower level in the adult.

We have made a series of analyses of the whole blood in the human subject and in dogs. These are given below.

Calcium Content of Human Blood at Different Ages in Per Cent.

No.	Sex.	Age.	CaO in Blood.
1.	f.	2	0·016
2.	m.	4	0·016
3.	f.	7	0·013
4.	m.	9	0·013
5.	f.	17	0·011
6.	m.	27	0·011

Calcium Content of Blood of Dogs at Different Ages in per Cent.

No.	Age.	CaO in Blood.
1.	11 weeks	0·019
2.	11 ,,	0·019
3.	11 ,,	0·013
4.	13 ,,	0·015
5.	13 ,,	0·020
6.	Adult	0·011 0·010
7.	Adult	0·011
8.	Adult	0·011
9.	Adult	0·012

These results seem to show that the calcium content of the blood is higher in young growing children and dogs than it is in the adult.

(b) *In Rachitic and in Normal Pups.*

The calcium content of the blood was also determined in the pups used in the experiments recorded in the *British Medical Journal* (25), and in those recorded in the *British Journal of Experimental Pathology* (13).

The following table gives the results:

Calcium Content of the Blood in the Rachitic and Normal Pups in per Cent.

Litter.	Controls.	Average per Litter.	Rachitic.	Average per Litter.	Age.
1	0·015 0·020	0·017	0·014 0·017 0·020 0·016 0·021 0·016	0·017	13 weeks
2	0·019 0·019 0·019	0·017	0·015 0·016 0·013 0·018	0·015	11 weeks
3 (*a*)			0·012		
(*b*)			0·012	0·012	20 weeks
(*c*)			0·011*		
4 (*a*)			0·011		
(*b*)			0·010		
(*c*)			0·011	0·010	17 weeks
(*d*)			0·011*		

* = rickets very slight.

Pups 3*c* and 4*d* appeared normal, but showed signs of commencing rickets by X-ray photographs although on post-mortem examination no marked softening of the bones was found. They are therefore included along with the rachitic.

These figures seem to show that in experimental rickets in dogs there is no decrease in the calcium content of the blood.

On account of the difficulty of obtaining a sufficient supply of blood for analysis from infants, we have been able to make only a few observations on the calcium content of the blood in spontaneous rickets, but the investigation is still in progress.

Conclusions.

1. Changes in bones, simulating somewhat those in rickets, can be caused by feeding on a calcium-low diet, but the condition is of the nature of osteoporosis and not true rickets.

2. The tissues other than bone in experimental rickets in dogs are not deficient in calcium.

3. The calcium content of the blood in experimental rickets in dogs shows no divergence from the normal.

4. No support is given to the view that rickets is due to a deficient supply of calcium to the bone.

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II. THE CALCIUM BALANCE IN NORMAL AND RACHITIC CHILDREN.

A. Introductory.

In the previous part evidence was adduced which seemed to negative the view that rickets is due to a failure in the supply of calcium.

Since in experimental rickets in dogs the amount of calcium in the tissues (muscle and brain) is not markedly decreased, the diminution in the calcium content of the bone would seem most probably to be due: (1) to a failure of the growing bone to fix the lime-salts, either (*a*) supplied in the food, or (*b*) made available by the process of decalcification by which spongy bone is produced, or (2) to an exaggeration of the process of decalcification. Although the onset of late rickets and the development of cranio-tabes at first sight would seem to indicate that increased decalcification alone may be operative, these conditions may just as well be explained by a failure to use, for fresh bone formation, the lime set free in the normal process of decalcification. The fact that the manifest changes are most marked at the growing ends of the bones is rather against the idea that the process is primarily one of decalcification.

The chief evidence against the decalcification theory is the contrast in the behaviour of the metabolism of calcium in rickets and in osteomalacia, diabetes, and fasting.

In osteomalacia there is an increased output of lime which may be so marked that more is excreted than is ingested, and apparently chiefly by the urine, so that a negative balance may be produced. Goldthwait, Painter, Osgood and McCrudden (1) record the results of a metabolism experiment extending over a period of eight days in a case of osteomalacia of sixteen years of age. The intake of lime was 4·56 grm. and the total output 5·66 grm., 1·80 grm. being present in the faeces and 3·85 grm. in the urine. Neumann (2) has also published a similar investigation extending over a period of six days, in which the total intake of lime was 2·965 grm., and the total output was 2·6 grm., 1·7 grm. being excreted by the urine and 0·9 grm. by the faeces.

In diabetic acidosis, too, there is an increased output of calcium, also mainly by the urine. Von Noorden (3) has observed its occurrence, and he quotes some observations by Gerhardt and Schlesinger to the effect that the daily intake of lime in one case was 0·81 grm., and the output 1·127 grm., 76 per cent. of which was excreted by the urine. These workers noted that the administration of 20 grm. of sodium bicarbonate per diem hardly altered the total excretion, but modified the proportion present in the urine and faeces, so that only 48 per cent. was excreted by the urine. Von Noorden holds that it is only when acidosis ensues in diabetes that decalcification occurs, but Kahn and Kahn (4) have

recorded in diabetes without acidosis a negative calcium balance which must indicate decalcification.

In rickets, there is, in marked contrast to the above, a decreased amount of lime in the urine and an increased amount in the faeces (Schabad (5)), and it has therefore usually been assumed that in this disease an amount of lime larger than normal is excreted by the intestinal tract, but the difficulty of determining how much of the calcium of the faeces has simply passed through the intestine unabsorbed and how much has been excreted into the gut has always left this question undecided. The recent work of Grosser (6) on the calcium metabolism in rickets under the administration of lime-salts shows that excretion by the intestine may take place to a large extent. His experiments consisted in the administration by the mouth and subcutaneously of various lime-salts to normal and rachitic children. Some of his series of observations extend over 40 days, and each was divided into periods of 3 or 4 days, for each of which estimations of the intake and of the output of calcium by urine and faeces are given. The chief excretion was usually in the period after that during which the lime-salt had been given. In one case 126 per cent. of the intake appeared in the faeces and 0·8 per cent. in the urine. In another case 107 to 127 per cent. of the intake appeared in the faeces, and between 0·8 and 1·7 per cent. in the urine. The increased excretion by the bowel indicated from these results is confirmed by another case in which 50 per cent. of the calcium was given subcutaneously, and yet 70 per cent. of the total daily intake appeared in the faeces and only 6·0 per cent. in the urine.

It will be shown later that the amount of calcium excreted by the gut depends largely upon the amount of faeces, but in Grosser's cases the daily weight of dried faeces was practically the same throughout the observations.

These results upon children confirm those previously obtained by Ragnar Berg upon himself (7).

Schabad (5), who supports the view that decalcification occurs in rickets, argues that this is indicated by the occurrence of a negative calcium balance, but, as already indicated, such a conclusion is not warranted. He made five investigations of progressive rickets, three of three days, one of five days, and one of seven days, and it was in his experiments of three days alone that he obtained a negative balance. The danger of drawing conclusions from such short metabolic studies will be dealt with later (p. 364).

Schabad also records (*loc. cit.*) the case of a rachitic child of 6,720 grm. in which he estimated the calcium of the body, and found that it amounted to between 21 and 22 grm., whereas the normal child at birth, weighing 3,000 grm., contains about 37·5 grm.; thus, without making allowance for the addition of calcium after birth, some 15 grm. had been lost from the body. He argues that the result indicates an exaggerated decalcification, but, as already indicated, the loss of calcium might just as well be explained by a failure of the growing bone to use the calcium set free by the normal process of decalcification in ossification.

With an increased decalcification an increased calcium content of the blood might be expected unless the lime is so quickly excreted that no time is given for its accumulation. In the previous paper we have shown that, in experimental rickets in dogs at least there is practically no change in the calcium content of the blood. In osteomalacia, on the other hand, a definite increase in the calcium of the blood has been recorded by Maurice Loeper and Béchamp (8), 100 c.c. of blood containing ·01 grm. of calcium, in contrast to ·0065 grm. to ·007 grm. in the normal individual.

The evidence is thus against rickets being due primarily to increased decalcification.

A failure to fix calcium by the bone-forming tissues may be due:

(1) To the calcium or some other constituent of bone, e.g. the phosphorus, being presented to it in abnormal form, so that the process of formation of the calcium complex characteristic of bone is prevented, or,

(2) To some change in the ossifying tissue by which the power of forming this calcium complex is lost.

Both of these might result from the existence of some generalized metabolic disturbance, which would thus bring the bone condition into accord with the general disturbance of health seen in rickets.

A study of the calcium balance cannot prove or disprove any of these possibilities, but, as a preliminary to an attempt to investigate them, it is necessary to have a knowledge of how far and in what respects the metabolism of calcium in rickets differs from the normal.

A very large number of observations upon this has been recorded. Some of the more important of these have been referred to in the introduction to 'A Study of Social and Economic Factors in the Causation of Rickets' (9).

A study of these records, however, shows that in many cases the conclusions drawn are unwarranted, because certain disturbing factors have not been sufficiently considered in the observations made. Of these we find that the following are the most important: (1) the short period of many of the studies; (2) the influence of age on retention of calcium; (3) the relationship of the retention of calcium to the intake; (4) the effect of the nature of the calcium compound ingested, and (5) the stage of the disease.

1. *The Danger of Short Period Studies of Calcium Metabolism. The Relationship of Calcium Output to the Weight of the Faeces.*

Consideration of the results of previous investigations and of our own early experiments has shown us that in the study of the metabolism of such a substance as calcium it is dangerous to draw conclusions from experiments extending over short periods such as three days. The difficulty of carrying on metabolic experiments on children for more prolonged periods probably accounts for so many workers being content with such brief studies.

As already indicated, the excretion of calcium in rickets, in contrast to that

in osteomalacia and diabetes, is mainly by the gut, some 96 per cent. of the whole being passed in the faeces.

One of us (J. S.) soon found that in each case the calcium formed a fairly fixed percentage of the dry faeces (Tables I, II, III, and IV), and, since the weight of faeces varies considerably from day to day, the calcium output also varies. Hence, if a day on which a large motion is passed falls within a short period of observation a fallacious negative balance may result.

The following observations illustrate these points, which are also substantiated by the results of studies recorded later in this paper. See also Charts I and II.

TABLE I (Waite). *Early Rickets.*

Amounts in Grm.

Day.	Intake CaO.	Wt. of Dry Faeces.	CaO in Faeces.	% of Dry Faeces.	Quantity Retained.
1	1·70	17·2	1·97	11·48	−0·27
2	1·70	16·4	1·68	10·24	0·02
3	1·70	13·8	1·29	9·38	0·41
4	1·70	11·25	0·84	7·50	0·86
5	1·70	11·25	0·84	7·50	0·86
6	1·70	16·6	1·64	9·88	0·06
7	1·70	3·9	0·36	9·40	1·34

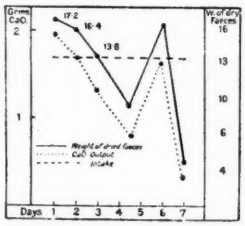

CHART I. Showing relationship of CaO to weight of faeces. Weight of CaO output in grm. on left ordinate. Weight of dried faeces in grm. on right ordinate. Days on abscissa. (CaO output drawn to eight times the scale of the dried faeces weight.) The average of 4 and 5 is expressed as a single point.

TABLE II (H.). *Normal.*

Amounts in Grm.

Day.	Intake CaO.	Wt. of Dry Faeces.	CaO in Faeces.	CaO % of Dry Faeces.	Quantity Retained.
1	1·81	5·0	0·765	15·33	1·045
2	1·67	10·0	1·430	14·33	0·240
3	1·74	4·0	0·664	16·66	1·076
4	1·83	14·8	2·131	14·47	−0·301
5	1·67	7·5	1·057	14·19	0·613
6	1·84	5·3	0·800	15·12	1·040
7	1·79	17·1	2·479	14·58	−0·689
8	1·67	7·1	1·036	14·61	0·634
9	1·72	12·5	1·875	15·00	−0·155
10	1·90	5·6	0·677	12·18	1·223
11	1·72	8·5	1·190	14·00	0·530
12	1·72	5·0	0·710	14·25	1·010

Had the first three days been taken alone, a positive balance of only 0·05 grm. per day would have appeared, while the last three days would have

indicated a daily positive balance of no less than 0·75 grm. In striking a balance the inclusion of the last day would introduce a manifest error.

But perhaps the most marked example is afforded by the study of H., ♀, $8\frac{3}{4}$ months old, where the increased excretion of CaO in the days when a large amount of faeces were passed is strikingly shown.

Had the study in this case been made upon the 7th, 8th, and 9th days, a negative balance of 0·210 grm., or 0·07 per day, would have appeared, while the next three days would have given a positive balance of 2·763 grm. or 0·921 per day.

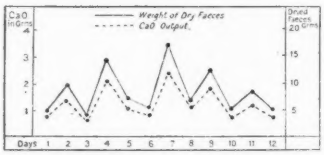

CHART II. Showing relationship between CaO output and the weight of dried faeces, in case of Child H. (CaO output drawn to four times the scale of weight of dried faeces.) Day periods on abscissa.

TABLE III (Calligan). *Tetany.*

Day.	Intake CaO.	Wt. of Dry Faeces	CaO in Faeces.	CaO % of Dry Faeces.	Quantity Retained.
1	3·38	27·8	2·79	10·05	0·59
2	3·38	22·6	1·77	7·86	1·51
3	3·38	20·5	2·32	11·34	1·06
4	3·38	6·8	0·77	11·39	2·61
5	3·38	20·7	1·95	9·30	1·43
6	4·50	26·4	3·04	11·53	1·46
7	4·50	25·2	2·85	11·34	1·65
8	4·50	23·7	2·92	12·34	1·58

TABLE IV (McArdle). *Rickets.*

Day.	Intake CaO.	Wt. of Dry Faeces.	CaO in Faeces.	CaO % of Dry Faeces.	Quantity Retained.
1	1·77	10·0	1·32	13·21	0.45
2	1·77	9·0	1·00	11·14	0·77
3	1·77	6·2	0·61	9·99	1·16
4	1·77	3·6	0·37	10·38	1·40
5 and 6	3·54	19·2	1·92	10·05	1·62
7	1·77	4·5	1·48	10·72	1·29

These results are fully borne out by an analysis of the cases recorded by Orgler (10).

Conclusion. Since the excretion of the calcium in the faeces varies with the weight of the dry faeces, and since the latter varies considerably from day to day, studies of calcium metabolism over periods of three days are unreliable.

2. *The Influence of Age on the Calcium Balance and on the Excretion by the Faeces and Urine.*

(A) *Age.*—In certain of the investigations recorded the influence of age upon the calcium metabolism has not been sufficiently recognized, and although rickets chiefly affects children under 3 years of age, the occurrence of cases of late rickets at a more advanced age renders it necessary to consider the normal retention of lime at different ages.

Many studies are available, but in comparing them with one another and with our own results, not only have the possible disturbing elements of differences in the diets and in the amount of calcium contained to be taken into account, but the differences in the weights of the individuals must also be considered.

To render a comparison possible the intake, output, and retention must therefore be expressed in relationship to unit of weight. Accordingly, not only in our own cases, but in our study of the results of others, we have, as far as possible, calculated the findings in terms of per kilo body weight.

Throughout this paper we use the terms 'utilization' of calcium and calcium 'available' to mean the difference between the calcium ingested and that excreted in the faeces. While in infants this practically represents the amount retained, since over 96 per cent. is excreted in the faeces, in older individuals this is not the case, since, as age advances, an increasing proportion is excreted in the urine. (See p. 370.)

(a) *Previous Investigations.*

Details with reference to authorship and place of publication, &c., of previous work considered by us are given in Appendix III. In the discussion of findings, and in the charts on pp. 368 and 369 this material has been combined and averages drawn.

The cases during infancy, i. e., until one year of age, have been divided into two groups according to whether the children were naturally or artificially fed, because, although the intake of calcium in the case of breast-milk is decidedly less than in the case of cows' milk, the utilization of the calcium, as shown by Langstein and Meyer (11), is better. The difference between the percentage retention of breast-fed and bottle-fed infants is made most striking when the amounts are expressed in terms of unit of body weight (Chart III).

The series of breast-fed infants considered comprised only children under six months of age. In the newborn infant the intake averaged 0·014 and the retention 0·013 grm. per kilo; under one month the intake was 0·08 and the retention 0·05 grm.; for children from one to three months the intake averaged 0·11 and the retention 0·041 grm.; and from three to six months of age the intake was 0·063 and the retention 0·030 grm. per kilo of body weight.

Studies of a much larger series of children (Chart III) fed upon cow's milk are available. The intake was very much greater, above one month being 0·12 to 0·21 grm. per kilo, but the retention, on the other hand, distinctly less, being between 0·021 and 0·032 grm. per kilo. In spite of the variation of intake and the declining intake per kilo from three months onwards, the retention per kilo remained remarkably constant. It would seem from these previous observations that in the healthy infant during the first year of life, although the retention varies to some extent with the intake, it is fairly constant, averaging between 0·02 and 0·03 per kilo of body weight.

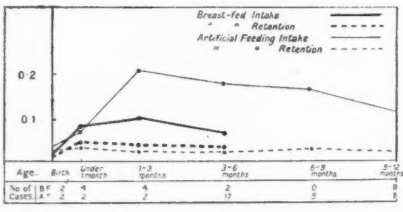
Breast-fed Intake
" " Retention
Artificial Feeding Intake
" " Retention
0·2
0·1
Age. Birth Under 1 month 1-3 months 3-6 months 6-9 months 9-12 months
No of Cases. B. 2 4 4 2 0 0
A. 2 2 2 17 9 5

CHART III. Showing average CaO intake and CaO retention, per kilo body weight at different ages, in healthy children fed on human and on cow's milk, recorded by previous investigators. Grm. per kilo body weight on ordinate. Age of children and number of cases on abscissa.

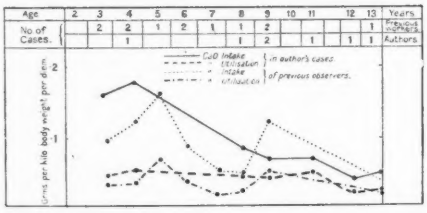
Age 2 3 4 5 6 7 8 9 10 11 12 13 Years
No of Cases. 2 2 1 2 1 1 1 2 1 1 1 1 Previous Workers
1 1 2 1 1 2 Authors
CaO Intake
CaO Utilisation
Intake
Utilisation
in author's cases
of previous observers.
Grms. per kilo body weight per diem
2
1

CHART IV. Showing relationship of utilization of CaO to intake in authors' healthy cases, compared with those recorded by previous observers (Ahlqvist, Schabad, and Herbst) from 2 to 13 years, expressed in grm. per kilo body weight per diem.

In healthy children over one year of age (Chart IV) the intake of calcium per kilo was found gradually to decline, reaching at 7 years about 0·05 grm., owing to the fact that as the children got older the calcium-rich milk became less and less the predominant constituent of the diet; nevertheless, the amount retained remained fairly constant, though varying somewhat with the intake. As age advanced the percentage utilization of the calcium was found to increase, so that on Chart IV the lines showing intake and output, though gradually declining, tend to converge.

(b) *Present Observations.*

We are fortunate in being able to record a very full series of observations on the calcium metabolism in normal individuals at different ages (Chart V). Those made on infants and children under 4 years of age were carried out specially

to afford a normal standard for the study of the metabolism in rickets, while those on older subjects were made in the course of an investigation on the digestibility of bread from flour of different milling standards (Appendices I and II).

The studies may be divided into four groups: (1) those on infants under one year; (2) those on children under 4 years of age on a diet chiefly of

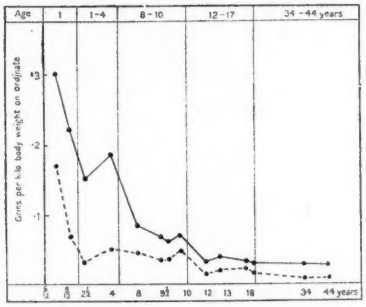

CHART V. Relationship of CaO intake to utilization in authors' healthy individuals from 6 months to 44 years. Grm. per kilo body weight on ordinate. Age on abscissa.

milk; (3) those on boys from 4 to 12 years, fed on bread and milk; and (4) those on older persons taking a more mixed diet. The results may be briefly summarized in the following table:

Calcium in Grm. per Kilo as CaO.

Age in Years.	Intake.	Output in Faeces.	% Utilized.
0–1	0·23	0·15	35
2–4	0·17	0·13	23
8–12	0·07	0·03	57
12–13	0·037	0·02	52
16–17	0·030	0·006	80
18–48	0·025	0·01	40

The utilization of calcium is thus fairly proportionate to the rate of growth, showing a marked increase beginning about the eighth year and reaching a maximum just before puberty. This, however, does not necessarily mean an increased retention since the excretion by the urine increases as age advances (p. 370).

In Charts IV and V these findings have been graphically represented. When the observations of previous workers are recalculated and drafted in the same way they are found to be in general accord with the authors' results.

Chart V shows a steady decline in intake as age advances, the fall being most rapid during the earlier years of life. The availability, generally, is proportionate to the intake. (See next section.)

(B) *The Relative Amount of Calcium excreted by the Faeces and Urine at Different Ages.*—Previous investigators have observed the fact that the proportion of calcium excreted by the urine increases as age advances.

This simply means that in older individuals any surplus absorbed over that

required for growth and metabolism of bone is got rid of by the kidneys instead of by the bowel as in infants. This is very clearly shown in the following table which gives the results of seven-day observations made upon two normal children, and upon five older males used for experiments on the digestibility of various breads.

CaO Excretion by Urine in Normal Individuals.

Name.	Age.	CaO in grms. In Diet.	CaO in grms. In Urine.	% Excreted by Urine.
Dodds	8	1·99	0·18	9·0
Lawson	9½	1·99	0·15	7·6
F. M.	12	1·22	0·09	7·3
Don. B.	13	1·25	0·11	7·4
J. W.	17	1·28	0·34	26·6
D. B.	34	1·22	0·27	21·6
J. R. T.	44	1·22	0·33	27·0

The comparatively large proportion of calcium excreted in the urine after the age at which growth has nearly ceased is clearly demonstrated. This leads to a decreased retention of the calcium absorbed.

Conclusions. 1. The large intake during the first year of life, about 0·2 grm. per kilo, is due to the purely milk diet. The retention or utilization is high and is almost 35 per cent. of the intake. This is considerably higher than the average of cases previously observed.

2. Between the age of 1 and 4 years, through the increased size of the child, the relatively lower caloric demands, and the fact that cereal foods are added to the milk, the intake of calcium is lower, about 0·17 grm., and the utilization is correspondingly reduced, being about 23 per cent. of the intake.

3. Between 8 and 12 years of age, the intake is still smaller, 0·07, but the amount utilized is hardly, if any, less than during the earlier age period, and there is thus a better percentage utilization of calcium—about 57 per cent.

4. Between 1 and 10 years a utilization of between 0·03 and 0·05 grm. CaO per kilo body weight seems to meet the requirements of the child.

5. From 12 to 13 years of age the intake per kilo body weight falls further (0·037), as does the utilization, but not proportionately, the percentage utilization of the calcium being still high—almost 52 per cent.

6. The intake per kilo remains about the same till just before puberty, when the utilization is still higher. It may amount to about 80 per cent. But at this period the excretion by the urine shows a marked increase.

7. In adult life the intake falls and the utilization is reduced.

8. The high intake of calcium in infants and young children on a diet of cow's milk is due to the proportion of calcium being unduly high in relationship to the energy value of the milk. Cows' milk has 0·14 per cent. of CaO, while human milk contains about 0·03 per cent., but the energy value per litre is practically the same.

3. *The Relationship of the Utilization of Calcium to the Intake.*

In comparing the investigations of different workers with one another it is found that the influence of the amount of calcium in the food per unit of body weight upon the calcium balance has not received due consideration.

The results just recorded on the effect of age on the utilization of calcium show that, calculated per kilo of body weight, there is, at least over short periods, not only a relationship between the age and the utilization of calcium, but also between the amount ingested and utilization. This is most strikingly shown in Cases 1 of the normal series, and in 2, 5, and 7 of the rachitic series (Summary Table, p. 378); and is also indicated in Chart VII, where the intake and utilization in both the normal and rachitic cases are arranged in order of intake, irrespective of age; and in Chart IV in which our own results and those based upon the recalculation of the results of previous investigators are compared.

In adults the same relationship between intake and availability or utilization holds, as will be seen by the following table constructed from our bread experiments. The number after the initial indicates the bread which was used. (Appendix I.)

Initials.	Age.	Intake.	Utilized.	% Utilized.
J. W. 1	17	0·037	0·033	83
J. W. 2	17	0·032	0·024	74
D. B. 1	33	0·032	0·026	58
J. B. 1	17	0·029	0·025	86
J. R. T. 1	43	0·028	0·018	50
J. R. T. 2	43	0·026	0·012	46
D. B. 2	33	0·024	0·015	59
J. B. 2	17	0·025	0·017	66
J. W. 3	17	0·025	0·016	65
J. B. 3	17	0·023	0·016	69
D. B. 3	33	0·022	0·009	39
J. R. T. 3	43	0·019	0·008	39

As to whether Stoeltzner's (*loc. cit.*) suggestion that the increased supply of calcium acts as a stimulant to ossification, and thus increases the deposition of calcified bone, is right, we have no evidence. There is, undoubtedly, evidence that there may be brought about a temporary accumulation of lime salts which, however, are later excreted. The results of many investigators suggest this, but perhaps the clearest evidence is afforded by those of Grosser (*loc. cit.*).

Conclusion. The utilization of calcium tends to vary directly with the supply in the food.

4. *The Character of the Food.*

Although most of the children who develop rickets are still upon a diet mainly consisting of milk, the possible effects of variation in the food constituents must be considered in comparing the results of different studies.

As already indicated, the percentage utilization of calcium in human milk is better than in cows' milk (p. 367). The reason for this is not apparent.

From experiments upon dogs fed upon horse-flesh Kochmann and Petzsch (12) concluded that an increase of the proteins, and the addition of starch or fat to the food leads to a smaller retention of calcium, but the results recorded hardly justify this conclusion. They argue that this is not due to decreased absorption but to some influence upon intermediate metabolism, by which more lime is set free from the store in the bones and excreted.

It is difficult to see how the absorption of lime from the gut can be modified by the protein or carbohydrate content of the diet, but the ready formation of insoluble calcium soaps of the higher fatty acids renders it possible that the amount of fat in the diet may modify the absorption of lime.

The fact that under normal conditions the faeces contain an amount of phosphoric acid sufficient to combine with nearly all the calcium as tri-calcium phosphate renders it improbable that calcium soaps are normally formed to an extent to carry off much of the calcium. The amount of calcium in such soaps is usually between 10 and 20 per cent., and thus generally over 80 per cent. is excreted as calcium phosphate.

Kochmann and Petzsch found that the addition of 50 grm. of fat to the diet of the dog, while decreasing the absorption of lime, did not alter the proportion of P_2O_5 to CaO in the faeces.

Telfer (13) finds that increasing the milk-fat from 21·6 grm. per diem to 43·2 grm. does not modify the absorption and retention of calcium.

The fatty acids are probably absorbed as rapidly as they are formed and only, as in the case of obstruction to the passage of bile to the intestine and probably in pancreatic disease when their amount in the gut is enormously increased, do they displace the phosphoric acid by forming calcium soaps. The phosphoric acid is then absorbed and excreted in the urine. This has been shown to be the case in congenital obliteration of the bile ducts by Telfer. (Paper appearing in *The Biochemical Journal.*)

Hutchison's observations (14) have demonstrated that in rickets there is no decrease in the digestion and absorption of fats.

The possibility of the disease being associated with an increased excretion of calcium soaps by the bowel may therefore be dismissed.

The contention of Orgler (15) and Freund (16) that certain fats have a more prejudicial action on the retention of lime than have others has been tested by Telfer (13) in this laboratory. His results show no differences in the calcium retention with similar amounts of butter-fat and of cod-liver oil.

Conclusions. 1. The calcium of human milk is utilized to a greater proportion than that in cows' milk.

2. The increase of milk-fat does not decrease the utilization of calcium in either normal or rachitic children since, apparently, the fatty acids are rapidly absorbed, and only about one-tenth of the total calcium is combined in soaps.

3. When the digestion and absorption of fat is arrested, as in obliteration of the bile ducts, the proportion of lime combined in soaps in the faeces is large, and a diminished utilization probably results.

5. *Stage of Disease.*

Some of the older workers on the metabolism in rickets gave too little consideration to the stage of the disease at which the observations were made.

Schabad (5) drew attention to the varying degree of retention of calcium according to the stage of the disease and produced evidence to show (1) that it is only in the early stages that a negative balance is obtained, but (2) that in fully developed rickets the retention is positive although below the normal, and (3) that in healing rickets the retention of calcium is definitely above the normal. These conclusions have been already referred to and the danger of accepting the results of short-period studies has been indicated.

From the chronic nature of the disease, it is clinically impossible to decide in any case of rickets whether the process is progressing or healing, in fact, it may be progressing at one place and healing at another, and therefore it is only on the grounds of probability that cases can be selected for investigation. It is, of course, more likely that in the younger cases the disease is early and progressive, while, in older children, there is always a greater possibility of the disease being either advanced or tending towards recovery, although it might be some time before the clinical changes are sufficiently marked to be appreciated. This is a criticism that may be raised against the selection of the series of cases recorded in this paper, but we purposely chose those with marked clinical signs and symptoms.

There is at least some indication that the most severe disturbances in metabolism may precede the appearance of symptoms. Birk and Orgler (17) record the case of a breast-fed infant which gave a negative calcium balance at the age of 1½ months, but which presented no clinical manifestations of rickets till the age of 4½ months, although at 2½ months and 4½ months metabolic studies revealed daily calcium retentions of 0·079 and 0·071 grm. We have also had the opportunity of making a somewhat similar observation. One of our cases (Waite), chosen as a normal control because of the absence of any physical signs of rickets, at the age of eight months gave a very low positive balance of 0·05 grm. per kilo per day with an intake of 0·283 grm., but on being seen a few months later presented a most severe degree of rickets.

In the series of investigations which are now in progress we are selecting only the youngest cases with any suspicion of the disease.

B. Comparison of the Calcium Balance in Normal and Rachitic Children.

In our series of observations, an attempt was made to guard against the various difficulties and fallacies to which attention has been drawn, as vitiating some of the previously recorded results.

(1) We have carried on the experiments for six or seven days when possible, and in the experiments of shorter duration we have had the patient upon the

diet for at least three days before the study was started. In two of the three-day observations a repetition of another three days was made.

It will at once be evident that many such prolonged studies must end in failure, some disturbance in the health of the child, e.g., vomiting, or some mistake in the feeding, or in the collection of the excreta, necessitating its termination and leading to a loss of its results.

(2) The records, both in normal and in rachitic children, have been arranged according to age so that they are comparable. They have been charted both according to age (Chart VI) and to intake of calcium (Chart VII).

(3) All the cases selected, except two of late rickets, were chosen because they appeared to be in the active stage of the disease with the characteristic symptoms well developed.

(4) The two cases of late rickets were studied on account of their comparative rarity, and on account of the possibility that in them evidence of abnormal decalcification might be discovered.

1. *Methods.*

We have estimated the calcium excreted by the faeces only, because in young children, especially female children, it is difficult to obviate some loss of urine. Since, however, in infancy, over 96 per cent. of the calcium is excreted by the bowel, the amount in the urine is of little significance. Schabad (*loc. cit.*) has shown that in the active stage of the disease the proportion of calcium in the faeces is higher than in the normal child. In the series of cases recorded by Orgler (15) the calcium in the urine in health was 1·9 per cent. of the total, whereas in rickets it was only 1·4 per cent. Such comparatively small amounts may safely be discarded, and indicate that the balance may be estimated from the calcium of the food and the faeces.

The difference between the intake in the food and the output in the faeces represents what may be called the 'available' calcium, or calcium utilized, although not necessarily the calcium retained. In comparing normal and rachitic children, as already indicated, the differences between the 'available' in the two groups may be taken as a measure of the differences between the amounts of calcium retained, except that the slightly lesser output by the urine in the case of rickets may possibly tend to magnify slightly the apparent retention.

(a) *Method of collecting faeces.* In older children no difficulty was experienced in collecting the faeces uncontaminated by urine, so long as the children were confined to bed.

For young male children, however, a special device called a 'metabolism bed' was made by having a couple of short mattresses, about 10 inches thick, placed in the bottom of the bed, and separated from one another by a distance of eight inches. The child is firmly fixed so that the buttocks are suspended over the space between these mattresses. The penis is placed into the end of

a piece of rubber-tubing, and the urine thus drained directly into a separate vessel, e.g., a urinal attached to the side of the bed. In this way urine and faeces may be collected separately.

The child is supported and kept in position by means of a firm calico arrangement, to which the child is fixed, stretched taut between the top and the bottom of the bed. The calico arrangement is composed of a body piece with

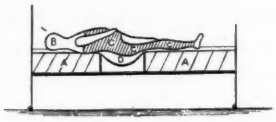

FIG. 1. Diagram of Metabolism Bed.
A.A. Mattresses with space between.
B. Patient.
C. Calico arrangement.
D. Jackinette pouch.

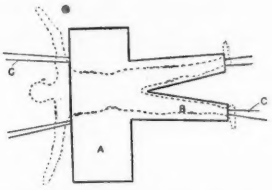

FIG. 2. Diagram of Calico Arrangement.
A. Body piece with binder.
B. Leg pieces.
C. Tapes for stretching between top and bottom of bed.

a binder attached so that the trunk is controlled, and two leg pieces to which the legs and thighs are bandaged with the legs held slightly apart. This piece of apparatus requires to be made to fit the child, special attention being paid to the size of the body piece and width of the leg pieces. The fork is situated at the lower end of the sacrum, just at the upper end of the natal cleft. (Figs. 1 and 2.)

A blanket is lightly placed over the child with a wire cage on top, which keeps the weight of any extra bed-clothes off the child and the apparatus.

It might be expected that a child confined in this way for periods sufficiently long (seven days) to collect material for metabolism experiments would be cross and irritable. Fortunately this is not the case, and the children so confined are usually quieter than the others in the ward. So well behaved are they that one married confrère considered the advisability of providing himself with one for home use. We have had normal children admitted to the wards, treated in this way for control experiments, visited by their parents during the course of the investigation, and in no case was any opposition raised to its continuance.

(b) *Control of diet.* In the earlier experiments, when the diet was composed entirely of milk, the exact quantity to be taken by the child was measured, and samples of the morning and evening milks examined. In the later experiments, one half ounce more than the amount of the feed was measured, thoroughly mixed, and the extra half ounce removed and retained for examination along with similar samples of all feeds for 24 hours. In the case of a mixed diet, two identical meals were prepared, one for the child and one for examination; any food which the child did not consume was also retained for examination.

(c) *Method for the determination of calcium.* The same method was

employed all through the work for determining the calcium content of food, faeces, brain, muscle, and blood.

A known weighed amount or volume of the material was dried, and then ignited in a silica basin until all or most of the carbon was driven off, care being taken not to employ too great or prolonged heating. The remainder was dissolved in hydrochloric acid and a little water, filtered and washed well. Any free carbon left after treatment with HCl was then further ignited and again treated with HCl and water and added to the first filtrate. It was found by this means that no calcium was caught by the carbon. To the filtrate excess of ammonium hydrate was added and then an excess of acetic acid. The calcium was thus brought into solution, and any precipitate of phosphate of iron was filtered off and well washed with hot water. Oxalic acid was added to the filtrate, precipitating the calcium as oxalate. The determination was finished in the usual way by solution in sulphuric acid and titration with N/10 potassium permanganate.

(d) *Test of Accuracy of the Process for estimating Amount of Calcium.*

100 c.c. normal ox blood taken	
Calcium oxide content (determined)	0·011 grms.
Calcium oxide (pure) added	0·100 ,,
Total CaO to be recovered	0·111 ,,
Number of grm. of CaO recovered	0·1105 ,,

The estimation was then carried out in the manner described above.

2. *Results.*

The main results of our investigations are given in the Summary Tables, p. 378, in Appendix II, and in Charts VI and VII.

As already indicated (p. 371), in health the most striking features of the calcium metabolism are the definite relationship which the 'utilization' bears to the intake (p. 366) and the gradual rise in the percentage utilization as age advances (see Charts IV and V).

In rickets the same features are observed. Chart VI, in which the individual rachitic figures are compared with the *averaged* figures for healthy children of the same age periods, shows a fairly close correspondence between the intake and retention per kilo body weight, and also a better percentage utilization of the lime as age advances. The correspondence between intake and retention is, however, not so absolute as in health. The older cases show a closer correspondence than the younger cases, a point which may be explained by the probability of the disease being more active and progressive in some of the latter. Perhaps the most striking feature of the rickets cases is the erratic behaviour of the utilization, e. g. a slightly increased intake may be accompanied sometimes by an increased and sometimes by a decreased utilization.

In no case was a negative balance observed, and the curve of the rachitic cases corresponds fairly closely with that found in health. In a few cases the utilization

departed from the normal standard, and an analysis of the case histories unfortunately does not always furnish an adequate explanation (see p. 378).

In Nos. 1 and 3 the retention is undoubtedly below the normal. No. 1 is the case previously referred to (p. 373), as probably resembling that described by Orgler, which gave a negative calcium balance before the clinical manifestation of rickets appeared. This was a child of eight months which seemed quite healthy and was used as a control, when a very low calcium utilization was found. On being seen four months later, however, very marked signs of rickets were present. At first sight this case would seem to indicate that the earliest sign of rickets may be a deficient calcium utilization, and to support the contention that during this period of the disease a low positive or even a negative calcium balance may occur. But the daily amount of dry faeces was high, and the large excretion of lime may be due to this.

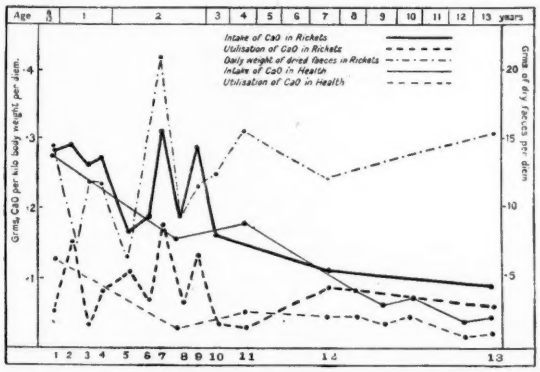

CHART VI. Showing intake and utilization of CaO in authors' cases of rickets arranged according to age and compared with averages of authors' healthy cases. Number of rachitic cases on abscissa.

Consideration of No. 3 must include discussion of 4, as these two experiments refer to the same child—4 following on 3 at an interval of two days. In this case the calcium intake and daily weight of dried faeces were practically identical during both studies, yet in the first period (3) the retention is low, and in the other period (4) within normal limits. This case was also a young child of fourteen months with an extreme degree of rachitic deformity. It illustrates the danger of short-period experiments. The average of the two periods is probably a more correct indication of the metabolism.

Cases 10 and 11 as shown in Chart VII, where the cases are arranged according to intake, seem to have abnormally low retentions, but reference to Chart VI, in which the cases are arranged according to age, demonstrates a normal retention, and this occurred in 11, in spite of a relatively high faecal output.

Studies 5, 12, and 13 all show utilizations somewhat above the normal. Nos. 5 and 6 must be considered together as they refer to two examinations in the same child at an interval of seven days. Here, with the higher intake, there

SUMMARY

No.	Name.	Age in Years.	Weight in kilos.	CaO Intake in Grm. Daily.	CaO Intake in Grm. Per Kilo per Day.	CaO Output in Grm. Daily.	CaO Output in Grm. Per Kilo per Day.
					Children Normal		
1.	Harby	$6\frac{1}{12}$	7·4	2·34	0·316	1·02	0·137
2.	H.	$8\frac{3}{12}$	7·7	1·75	0·228	1·23	0·159
3.	Brown	$2\frac{1}{2}$	12·8	2·02	0·158	1·64	0·128
4.	Bryson	4	15·9	2·86	0·180	2·01	0·126
5.	Dodds	8	24·0	1·99	0·083	0·87	0·037
6.	Lawson	$9\frac{1}{2}$	28·0	1·99	0·071	0·95	0·034
7.	Alexander	$9\frac{1}{2}$	26·0	1·72	0·066	0·72	0·027
8.	Jack	10	27·0	1·92	0·071	0·65	0·024
					Children and Adults		
9.	J. W.	16	51·0	1·90	0·037	0·22	0·004
10.	J. B.	16	53·0	1·57	0·029	0·19	0·003
11.	D. B.	33	57·0	1·77	0·031	0·74	0·013
12.	J. R. T.	43	62·0	1·77	0·028	0·88	0·014
9*a*.	J. W.	16	51·0	1·64	0·032	0·43	0·008
10*a*.	J. B.	16	53·0	1·31	0·025	0·44	0·008
11*a*.	D. B.	33	57·0	1·51	0·026	0·82	0·014
12*a*.	J. R. T.	43	62·0	1·51	0·024	0·61	0·009
13.	F. M.	12	35·1	1·22	0·034	0·57	0·016
14.	Don. B.	13	30·1	1·25	0·041	0·63	0·020
9*b*.	J. W.	17	51·0	1·28	0·025	0·45	0·009
10*b*.	J. B.	17	53·0	1·25	0·023	0·38	0·007
11*b*.	D. B.	34	57·0	1·25	0·021	0·76	0·013
12*b*.	J. R. T.	44	62·0	1·22	0·019	0·74	0·012
					Children with Rickets		
1.	Waite	$\frac{6}{12}$	6·0	1·70	0·283	1·37	0·228
2.	McArdle	$\frac{13}{12}$	6·1	1·77	0·290	0·82	0·134
3.	Wilson (1)	$1\frac{1}{12}$	6·15	1·63	0·265	1·46	0·237
4.	Wilson (2)	$1\frac{4}{12}$	6·15	1·69	0·275	1·19	0·193
5.	Young (1)	2	7·2	1·20	0·166	0·40	0·055
6.	Young (2)	2	7·2	1·34	0·186	0·86	0·119
7.	Crombie	2	9·4	2·98	0·317	1·35	0·144
8.	Duncan	$2\frac{2}{12}$	8·2	1·5	0·183	1·0	0·122
9.	McNeil	$2\frac{1}{4}$	6·3	1·83	0·290	0·97	0·154
10.	Scully	3	9·0	1·43	0·159	1·14	0·127
11.	Judge	4	11·0	1·64	0·149	1·32	0·120
							Late
12.	Brown	7	14·2	1·60	0·113	0·43	0·030
13.	Campbell	13	37·2	3·30	0·088	0·78	0·021

TABLES.

mainly on Milk Diet.

CaO Available in Grm.			Faeces in Grm.			Diet (Milk in c.c. Bread in grm. Butter in grm.) per Day.	Duration of Experiment in Days.
Daily.	Per Kilo per Day.	%	Daily Weight	Per Kilo per Day.	% of CaO.		
1·32	0·178	56·4	13·10	1·77	7·80	Milk, 1376 with a little virol	5
0·52	0·069	29·7	8·50	1·10	14·56	Milk, 1000	12
0·38	0·030	18·8	8·15	0·64	20·21	Milk, 1190, S. Laura	4
0·85	0·054	29·7	12·80	0·80	15·67	Milk, 1701, S. Laura	4
1·10	0·046	55·3	7·80	0·32	11·39	Milk, 1000; Bread, 225; Butter, 25	7
1·04	0·037	52·2	8·60	0·31	11·00	Milk, 1000; Bread, 225; Butter, 25	7
1·00	0·039	58·1	9·80	0·38	7·40	Milk, 1000; Bread, 23; Butter, 2	7
1·27	0·047	66·1	8·50	0·31	7·70	Milk, 1,129	3
on Bread Diets.							
1·68	0·033	88·4	23·20	0·45	0·96	Bread I	7
1·38	0·026	87·3	17·00	0·32	1·14	„ „	7
1·03	0·018	58·2	30·90	0·52	2·43	„ „	7
0·89	0·014	50·2	34·20	0·55	2·60	„ „	7
1·21	0·024	73·8	39·00	0·76	1·12	Bread II	7
0·87	0·017	66·4	38·00	0·71	1·17	„ „	7
0·69	0·012	45·7	47·90	0·82	1·73	„ „	7
0·90	0·015	59·6	36·10	0·70	1·70	„ „	7
0·65	0·018	53·3	22·10	0·63	2·66	Bread III	7
0·62	0·021	49·5	28·50	0·94	2·24	„ „	7
0·83	0·016	64·8	25·10	0·50	1·82	„ „	7
0·87	0·016	69·5	26·00	0·50	1·45	„ „	7
0·49	0·008	39·2	30·24	0·53	2·52	„ „	7
0·48	0·007	39·3	26·50	0·43	2·80	„ „	7
chiefly on Milk Diet.							
0·33	0·055	19·4	2·4	0·4	9·58	Milk, 1000	6
0·95	0·156	53·1	1·2	0·2	10·58	Milk, 1041	7
0·17	0·028	10·4	1·9	0·31	12·6	Milk, 931	3
0·50	0·082	29·5	1·9	0·31	10·0	Milk, 931; Bread, 62; Butter, 6	3
0·80	0·111	66·6	0·9	0·12	6·16	Milk, 883; Bread, 675; Butter, 8	3
0·48	0·067	35·8	1·7	0·24	7	Milk, 769; Bread, 81; Butter, 9	3
1·63	0·173	54·6	2·2	0·23	6·43	Milk, 1753	9
0·50	0·061	33·3	1·2	0·15	10·50	Milk, 961	4
0·86	0·136	47·0	1·7	0·27	8·40	Milk, 1000; porridge, 72·4	6
0·29	0·032	20·2	1·4	0·15	9·18	Milk, 664; Bread, 84; Butter, 9	3
0·32	0·029	19·5	1·5	0·14	8·45	Milk, 940; Bread, 114; Butter, 12	4
Rickets.							
1·17	0·083	73·1	0·8	0·06	3·50	Milk, 997; Bread, 107; Butter, 10	about 3
2·52	0·067	76·3	0·4	0·01	5·04	Milk, 1247; Bread, 108; Butter, 10	„ 3

is a lower retention, in spite of the fact that for three days previous to the second period (6) and during the period the child was receiving phosphorated oil and cod-liver oil. The difference between the faecal output during the two periods explains this—the weight of the dried faeces during the second period being practically double that during the first. In estimating the influence of cod-liver oil and phosphorus on the utilization of calcium, the large somewhat loose motions which frequently accompany their administration—the persistence of which sometimes necessitates the discontinuance of the treatment—must be kept in mind.

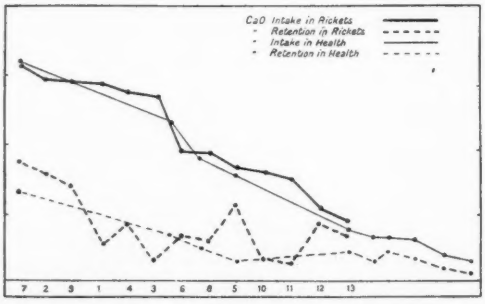

CHART VII. Showing relationship of CaO retention to intake, expressed in grm. per kilo body weight, in authors' cases of rachitic and healthy children, arranged in order of intake. CaO in grm. per kilo body weight on ordinate. No. of cases on abscissa.

Nos. 12 and 13 were examples of late rickets in children of seven and thirteen years respectively that came under observation during the summer at a season when the disease tends towards spontaneous recovery. In No. 12 the symptoms were of nine months' duration, and in No. 13 of four months' duration, but both children greatly improved during the short period they were under observation. The high retention may in part be explained by the retrogressive nature of the lesions, but the better utilization of the lime at this age must also be borne in mind.

The results of previous workers have given rise to the general assumption that a negative balance is not infrequently obtained, and undoubtedly many experiments have been published which record it. But, as already stated, in many of the series the period of the investigation was too short, e. g. in Schabad's series it was in three-day experiments that negative balances were obtained. In other cases the negative balance could be explained by the large excretion of faeces. Chart VIII shows the maximal and minimal calcium utilization calculated from these cases, both healthy and rickety, expressed per kilo of body weight, arranged according to age. It will be seen that negative balances are recorded both in health and in rickets, and we have obtained similar results in short-period studies. In the face of such findings it cannot be maintained that a negative balance is characteristic of any stage of rickets.

In Appendix III will be found details with reference to authorship, place of

publication, diet, faecal output, &c., with the intake and output of calcium expressed per kilo body weight.

Since our work was completed we have read a paper by Holt, Courtney, and Fales (18) upon the 'Calcium Metabolism of Infants and Young Children'. From the results recorded they draw certain definite and far-reaching conclusions, but the only record of the duration of the periods of study is a statement in a previous paper upon Fat Metabolism ('Fat in the Stools of Breast-Fed Infants', p. 8) (19), where it is said: 'In eleven instances, not only was a record of the exact daily

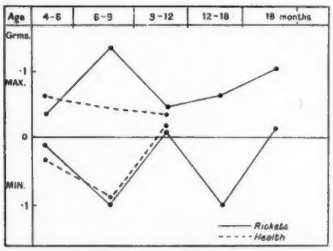

CHART VIII. Showing maximal positive and negative retentions of CaO in health and rickets recorded by various authors. Age on abscissa. Grm. CaO per kilo body weight on ordinate.

fat intake obtained but the stools were collected for definite periods, twenty-four or forty-eight hours.'

In reply to a letter sent to Dr. Holt asking him to let us know the duration of the studies, he was good enough to write as follows: 'In most cases the values reported are averages for two or three days; frequently for longer periods. The values for infants are mostly for three- and four-day periods; those for older children nearly all two or three days. Values for children with rickets or chronic intestinal indigestion were usually four-day periods.' The periods of study seem to us too brief. It is to be hoped that in a future publication the details of these experiments will be published so that one may be enabled to estimate the value of the conclusions.

A consideration of our results and of the work of previous investigators which we have analysed does not seem to indicate the profound disturbance in the calcium metabolism which many have assumed to be characteristic of rickets. As already indicated, we have not in any case found a negative balance over periods adequately long to allow of a reliable conclusion being drawn. In the early stages of the disease the positive balance may be low, indicating a lowered fixation of lime-salts in the bones, but as the process advances the approach of calcium balance to that in health seems to indicate that the process may still be advancing in one region while recovery may be taking place in another. While in severe cases the implication of the bone may be general, in most cases, as clinical experience indicates, it is more marked in some bones than in others.

Of the calcium taken in the food as cows' milk, only some 0·02 grm. per kilo seems capable of being utilized even in the normal infant. How much is actually absorbed from the bowel and how much is excreted into it we do not know.

In rickets the disturbance in the utilization is less marked than might be expected. In the four normal cases under four years of age, the utilization averaged 33·6 per cent. of the intake, corresponding very closely with Ahlqvist's results (20). In the eleven rachitic cases it was 35·4 per cent. In the four normal cases between eight and ten years, the utilization averaged 58 per cent. In the two cases of late rickets, aged seven and thirteen years, it averaged 74·7 per cent.

If the cases, normal and rachitic, recorded by Rothberg, Orgler, Schabad, Cronheim and Müller, Birk and Klotz, are arranged so that the ages of the two groups roughly correspond, 33 studies of 14 normal children and 25 studies of 14 rachitic children, all between $2\frac{1}{2}$ months and $10\frac{1}{2}$ months, are available for comparison.

	Non-rachitic.			Rachitic.		
Author.	Age.	Average Daily Intake.	Average Daily Retention.	Age.	Average Daily Intake.	Average Daily Retention.
	months.			months.		
Rothberg	$5\frac{1}{2}$	0·26	0·039	4	0·22	0·027
				$4\frac{1}{2}$	0·11	−0·013
				9	0·12	0·014
Orgler	$2\frac{1}{2}$	0·18	0·032	$4\frac{1}{2}$	0·06	0·020
	$2\frac{1}{2}$	0·25	0·027	$4\frac{1}{2}$	0·20	0·022
	$5\frac{1}{2}$	0·18	0·019	$6\frac{1}{2}$	0·17	0·044
	$5\frac{1}{2}$	0·20	−0·035	$6\frac{1}{2}$	0·20	0·061
	$6\frac{1}{2}$	0·18	0·019	$7\frac{1}{2}$	0·12	−0·096
	$6\frac{1}{2}$	0·25	−0·094	$7\frac{1}{2}$	0·18	0·009
Schabad	$3\frac{3}{4}$	0·047	0·023	5	0·05	0·026
				5	0·22	0·02
				6	0·05	0·013
Cronheim and Müller	4	0·22	0·044	6	0·22	0·082
	4	0·22	0·042	6	0·22	0·032
	4	0·22	0·020	6	0·21	0·064
	4	0·22	0·058	6	0·19	0·073
	4	0·22	0·029	6	0·21	0·046
	4	0·18	0·002	6		
	4	0·18	0·028			
	4	0·18	0·020			
	4	0·18	0·018			
	4	0·16	0·005			
	4	0·18	0·059			
	4	0·19	0·060			
	6	0·19	0·011			
	6	0·19	0·030			
Birk	9	0·12	0·056	8	0·11	0·002
	9	0·16	0·071	8	0·10	0·010
	$10\frac{1}{2}$	0·14	0·030	8	0·10	−0·008
	$10\frac{1}{2}$	0·13	0·032	8	0·09	0·006
Klotz	7	0·11	0·008	$9\frac{1}{2}$	0·14	−0·012
	7	0·13	0·008	$9\frac{1}{2}$	0·16	0·03
	9	0·10	0·005	$9\frac{1}{2}$	0·17	0·02
	9	0·09	0·004	$9\frac{1}{2}$	0·14	−0·003
	9	0·08	0·007			

Averages.	Non-rachitic.		Rachitic.	
	Intake.	Retention.	Intake.	Retention.
Rothberg	*(1) 0·26	0·039	(3) 0·15	0·009
Orgler	(3) 0·21	−0·005	(3) 0·15	0·010
Schabad	(1) 0·047	0·023	(3) 0·20	0·012
Cronheim and Müller	(4) 0·19	0·030	(2) 0·21	0·059
Birk	(2) 0·14	0·047	(2) 0·10	0·002
Klotz	(3) 0·10	0·006	(3) 0·15	0·009
Average =	(14) 0·16	0·02	(16) 0·14	0·017

* Number of *Cases* averaged.

This shows a percentage retention of 12·5 per cent. in case of the normal and of 12·1 per cent. in the rachitic.

The whole trend of the evidence suggests that the disturbance in the metabolism of calcium is probably not the primary factor in the disease, but that it is secondary to some other error of metabolism which is both the cause of the disturbance in the process of ossification and of the general symptoms of the disease.

3. *Conclusions.*

1. The 'utilization' of calcium, i. e. the difference between the intake in the food and the excretion in the faeces, in health and in rickets is fairly proportionate to the intake, but in rickets the parallelism is not so strict as in health.

2. The utilization of calcium in health and in rickets is influenced by age, the percentage utilization increasing with age up to thirteen years, but, since the excretion by the urine likewise increases, this does not necessarily mean increased retention (see p. 370).

3. The percentage of calcium in the dry faeces is a more or less fixed proportion, especially for each individual, and hence the amount excreted varies with the weight of dry faeces. Short studies of calcium metabolism are therefore of little value.

4. In rickets the utilization and retention of calcium in some cases falls below the normal, and these would seem to indicate a more progressive stage of the disease.

5. In other cases of rickets, especially in those of some duration, the retention of calcium may be above the normal for that age, probably indicating the stage of recovery.

Our thanks are due to Miss Agnew for the preparation of Appendix III.

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Appendix I.

Bread Experiments.

The results here recorded were obtained during a study of the digestibility of breads made from flours of different milling standards, and of mixtures of flours from wheat and maize (Report by the Food (War) Committee of the Royal Society on the Digestibility of Breads) (3206).

The breads used were:

Bread I. 80 per cent. milled wheat-flour.
Bread II. 90 per cent. milled wheat-flour.
Bread III. 80 per cent. wheaten-flour and 20 per cent. maize-flour.

Diets with the amount of calcium determined in the different constituents—

Bread I.

	Daily.	CaO.
Bread	800 grm.	0·78 grm.
Mince	150 „	0·13 „
Margarine	50 „	0·00 „
Jelly	50 „	0·05 „
Café au Lait	90 „	0·48 „
Chocolate	75 „	0·13 „
Cheese	75 „	0·33 „
		1·90 „

Bread II.

	Daily.	CaO.
Bread	800 grm.	0·46 grm.
Mince	130 „	0·11 „
Margarine	50 „	0·00 „
Jelly	40 „	0·04 „
Café au Lait	90 „	0·48 „
Chocolate	30 „	0·13 „
		1·22 „

Bread III.

	Daily.	CaO.
Bread	800 grm.	0·46 grm.
Mince	130 „	0·11 „
Margarine	50 „	0·00 „
Jelly	40 „	0·04 „
Café au Lait	90 „	0·48 „
Chocolate	30 „	0·13 „
		1·22

Appendix II.

Details of Individual Studies.

Normal.

Name.	Age.	Days.	CaO grm. In Diet.	CaO grm. In Faeces.	CaO grm. Available.	Dried Faeces grm. Weight.	Dried Faeces grm. % CaO.
James Harby	6½ months	1	2·34	0·75	1·59	10·7	7·00
		2	2·34	1·10	1·24	12·0	9·24
		3	2·34	1·29	1·05	15·0	8·62
		4	2·34	1·03	1·31	14·7	7·00
		5	2·34	0·94	1·40	13·2	7·14
H.	8¾ months	1	1·81	0·765	1·045	5·0	15·33
		2	1·67	1·430	0·240	10·0	14·33
		3	1·74	0·664	1·076	4·0	16·66
		4	1·83	2·131	−0·301	14·8	14·47
		5	1·67	1·057	0·613	7·5	14·19
		6	1·84	0·800	1·040	5·3	15·12
		7	1·79	2·479	−0·689	17·1	14·58
		8	1·67	1·036	0·634	7·1	14·61
		9	1·72	1·875	−0·155	12·5	15·00
		10	1·90	0·677	1·223	5·6	12·18
		11	1·72	1·190	0·530	8·5	14·00
		12	1·72	0·710	1·010	5·0	14·25
Andrew Brown	2 6/12	1	2·02	2·32	−0·30	11·2	20·72
		2	2·02	1·95	0·07	9·4	20·87
		3	2·02	0·30	1·72	1·5	20·21
		4	2·02	1·99	0·03	10·5	19·04
Charles Bryson	4	1	2·86	3·01	−0·15	19·2	15·76
		2	2·86	0·25	2·61	1·7	15·14
		3	2·86	2·83	0·03	17·2	16·57
		4	2·86	1·97	0·89	13·0	15·20
Dodds	Male 8	7	1·99	0·89	1·10	7·8	11·39
Lawson	,, 9 6/12	7	1·99	0·95	1·04	8·6	11·00
Alexander	,, 9 6/12	7	1·72	0·72	1·00	9·8	7·40
Jack	,, 10	3	1·92	0·65	1·27	8·5	7·70
F. M. (III)	,, 12	7	1·22	0·58	0·64	22·1	2·66
Don B. (III)	,, 13	7	1·25	0·63	0·62	28·5	2·24
J. W. (II)	,, 16	7	1·64	0·43	1·21	39·0	1·12
J. B. (II)	,, 16	7	1·31	0·44	0·87	38·0	1·17
D. B. (II)	,, 33	7	1·51	0·82	0·69	47·9	1·73
J. R. T. (II)	,, 43	7	1·51	0·61	0·90	36·1	1·70
J. W. (I)	,, 16	7	1·90	0·22	1·68	23·2	0·96
J. B. (I)	,, 16	7	1·57	0·19	1·38	17·0	1·14
D. B. (I)	,, 33	7	1·77	0·74	1·03	30·9	2·43
J. R. T. (I)	,, 43	7	1·77	0·88	0·89	34·2	2·60
J. W. (III)	,, 17	7	1·28	0·45	0·83	25·1	1·82
J. B. (III)	,, 17	7	1·25	0·38	0·87	26·0	1·45
D. B. (III)	,, 34	7	1·25	0·76	0·49	30·24	2·52
J. R. T. (III)	,, 44	7	1·22	0·74	0·48	26·5	2·80

Normal (continued).

Name.	Age.	Weight Kilos.	Intake. Daily.	Intake. Per Kilo per Day.	Output. Daily.	Output. Per Kilo per Day.	Available. Daily.	Available. Per Kilo per Day.	Available. %	Dried Faeces. Daily Weight.	Dried Faeces. Per Kilo per Day.	Dried Faeces. % of CaO.	Diet.	Duration in Days.
J. W.	16	51·0	1·90	0·037	0·22	0·004	1·68	0·033	88·4	23·20	0·45	0·96	Bread I	7
J. B.	16	53·0	1·57	0·029	0·19	0·003	1·38	0·026	87·3	17·00	0·32	1·14	,,	7
D. B.	33	57·0	1·77	0·031	0·74	0 013	1·03	0·018	58·2	30·90	0·52	2·43	,,	7
J. R. T.	43	62·0	1·77	0·028	0·88	0·014	0·89	0·014	50·2	34·20	0·55	2·60	,,	7
J. W.	16	51·0	1·64	0·032	0·43	0·008	1·21	0·024	73·8	39·00	0·76	1·12	Bread II	7
J. B.	16	53·0	1·31	0·025	0·44	0·008	0·87	0·017	66·4	38·00	0·71	1·17	,,	7
D. B.	33	57·0	1·51	0·026	0·82	0·014	0·69	0·012	45·7	47·90	0·82	1·73	,,	7
J. R. T.	43	62·0	1·51	0·024	0·61	0·009	0·90	0·015	59·6	36·10	0·70	1·70	,,	7
F.M.	12	35·1	1·22	0·034	0·57	0·016	0·65	0·018	53·3	22·10	0·63	2·66	Bread III	7
Don. B.	13	30·1	1·25	0·041	0·63	0·020	0·62	0·021	49·5	28·50	0·94	2·24	,,	7
J. W.	17	51·0	1·28	0·025	0·45	0·009	0·83	0·016	64·8	25·10	0·50	1·82	,,	7
J. B.	17	53·0	1·25	0·023	0·38	0·007	0·87	0·016	69·5	26·00	0·50	1·45	,,	7
D. B.	34	57·0	1·25	0·021	0·76	0·013	0·49	0·008	39·2	30·24	0·53	2·52	,,	7
J. R. T.	44	62·0	1·22	0·019	0·74	0·012	0·48	0·007	39·3	26·50	0·43	2·80	,,	7

Rickets.

Name.	Age.	No. of Days.	CaO grm. In Diet.	CaO grm. In Faeces.	CaO grm. Available.	Diet. Nature.	Diet. Amount per day grm. c.c.	Dried Faeces grm. Daily Weight.	Dried Faeces grm. % CaO.
Wait	$\frac{8}{12}$	1	1·70	1·97	− 0·27	Milk	1000	17·2	11·48
		2	1·70	1·68	0·02		1000	16·4	10·24
		3	1·70	1·29	0·41		1000	13·8	9·38
		4 and 5	3·40	1·68	1·72		1000	11·25	7·50
		6	1·70	1·64	0·06		1000	16·6	9·88
		7*	1·70	0·36	1·34		1000	3·9	9·40
McArdle	$\frac{13}{12}$	1	1·77	1·32	0·45	Milk	1041	10·0	13·21
		2	1·77	1·00	0·77		1041	9·0	11·14
		3	1·77	0·61	1·16		1041	6·2	9·99
		4	1·77	0·37	1·40		1041	3·6	10 38
		5 and 6	3·54	1·92	1·62		1041	9·6	10·05
		7	1·77	0·48	1·29		1041	4·5	10·72
Wilson (I)	$1\frac{4}{12}$	3	1·63	1·46	0·17	Milk	1. 1083 2. 826 3. 997 av. 968	1. 9·0 2. 11·5 3. 16·0 av. 12·2	12·06
Wilson (II)	$1\frac{4}{13}$	3	1·69	1·19	0·50	Milk, Bread,	1. 912+85	1. 16·5	10·0

* This day is not included in the summary average.

* This day is not included in the summary average.

Wilson (II) 2 days after (I)	$1\frac{4}{12}$	3	1·69	1·19	0·50	Milk, Bread, and Butter	1. 912+85 2. 912+59 3. 969+60·5 av. 931+68·1	1. 16·5 2. 11·0 3. 8·2 av. 11·9	10·0
Young (I)	2	3	1·2	0·4	0·8	Milk, Bread, and Butter	1. 741+110 2. 655+ 64 3. 655+ 77 av. 683+ 83	1. 10·5 2. 3·5 3. 6·0 av. 6·7	6·16
Young (II) 2 days after (I)	„	3	1·34	0·86	0·48	Milk, Bread, and Butter + 3 drm. per day of Olei phos.	1. 855+ 78 2. 570+ 89 3. 883+103 av. 769+ 90	1. 15·0 2. 7·0 3. 15·0 av. 12·3	7·0
Crombie	2	9	2·98	1·35	1·63	Milk	1753	21·0	6·43
Duncan	$2\frac{2}{12}$	4	1·5	1·0	0·5	Milk	1. = 855 2. = 912 3. = 1111 4. = 969 av. 961	1. = 8·5 2. = 9·5 3. = 12·3 4. = 8·2 av. 9·6	10·50
McNeil	$2\frac{3}{12}$	6	1·83	0·97	0·86	Milk and Porridge	av. 1000 „ 72·4	11·6	8·40
Scully	3	3	1·43	1·14	0·29	Milk, Bread, and Butter	1. 712+105 2. 627+109 3. 655+ 66 av. 664+ 93	1. 20 2. 7·9 3. 9·4 av. 12·4	9·18
Judge	4	3	1·64	1·32	0·32	Milk, Bread, and Butter	1. 997+125 2. 855+139 3. 969+114 av. 940+126	1. 12 2. 25 3. 10 av. 15·7	8·45
Late Rickets.									
Brown	7	3	1·60	0·43	1·17	Milk, Bread, and Butter	av. 997 av. 117	12·3	3·50
Campbell	13	3	3·3	0·78	2·52	Milk, Bread, and Butter	1. 1339+112 2. 1243+130 3. 1158+112 av. 1246+118	1. 14·2 2. 13·5 3. 18·7 av. 15·5	5·04

Appendix III.

Records of Previous Investigations of Calcium Metabolism from which Charts IV and VI were constructed.

Author.	Reference.	Name.	Age.	Condition.	Diet.	Average Wt. in Grm.	Duration of Experiment in Days.	Average Daily Wt. of Dried Faeces in Grm.	Average Daily CaO Intake per Kilo Body Wt. in Grm.	Average Daily CaO Retention per Kilo Body Wt. in Grm.
Birk	*Monats. f. Kinderh.*, Leipz. u. Wien, 1910, ix. 595	I	Newborn	Healthy	Colostrum	3870	5	2·44	0·019	0·014
,,	,, ,, ,, ,,	III	,,	,,	Human milk	3470	4	3·22	0·018	0·012
,,	,, ,, ,, 1911, x. 1	I (*a*)	,,	,,	½ milk + ½ water + 5 % milk sugar	3620	3	3·4	0·04	0·025
,,	,, ,, ,, ,,	II (*a*)	,,	,,	,, ,,	3120	2½	4·5	0·28	0·017
,,	,, ,, ,, ,,	II (*b*)	4 d.	,,	,, ,,	3030	2	5·5	0·63	−0·003
Michel	*L'Obstétrique*, 1896 (quoted by Schabad)	I	5 d.	,,	Human milk	3770	3	—	0·07	0·055
,,	,, ,, ,, ,,	III	5 d.	,,	,, ,,	2730	4	—	0·09	0·047
Birk	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 1	I (*b*)	6 d.	,,	½ milk + ½ water + 5 % milk sugar	3560	3	2·73	0·07	0·031
Michel	*L'Obstétrique*, 1896 (quoted by Schabad)	IV	7 d.	,,	Human milk	3590	6	—	0·08	0·054
,,	,, ,, ,, ,,	II	11 d.	,,	,, ,,	4440	3	--	0·07	0·045
Schlossmann	*Arch. f. Kinderh.*, Stuttg., 1904, xl. 1	Kubitz	1 m.	,,	,, ,,	2480	5	—	0·14	0·06
,,	,, ,, ,, ,,	Kriesch	1¾ m.	,,	,, ,,	4200	5	—	0·1	0·04
,,	,, ,, ,, ,,	Winter	1¾ m.	,,	,, ,,	4540	5	—	0·09	0·05
Tobler u. Noll	*Monats. f. Kinderh.*, Leipz. u. Wien, 1910 ix. 210	Kurt K.	2¼ m.	,,	,, ,,	4000	6	4·0	0·06	0·013
Orgler	,, ,, 1911, x. 373	Herbert G. (1)	2½ m.	,,	½ milk + ½ *Schleim* + 5 % sugar	3885	3	5·5	0·18	0·032
,,	,, ,, ,, ,,	Herbert G. (2)	2½ m.	,,	Same diet + 1 gr. calc. acet. p. d.	4015	3	6·1	0·25	0·027
Michel et Perret	*Bull. de la Soc. d'Obstét. de Paris*, 1899 (quoted by Schabad)	—	3 m.	,,	Human milk	4760	3	—	0·08	0·037
Meyer	*Biochem. Zeitsch.*, Berlin, 1908, xii. 422	Kind A. (1)	3 m.	,,	Milk, *Haferschleim*, sugar	5690	3	2·64	--	0·01
Bruck	,, ,, ,, ,,	Kind A. (2)	3 m.	,,	Milk, *Haferschleim*, sugar	5680	3	2·89	—	0·01

Bruck	*Monats. f. Kinderh.*, Leipz. u. Wien, 1908, vi. 570	—	3 m.	„	Milk, *Mehlsuppe*, sugar	3400	4	—	0·087	0·043
Schabad	*Arch. f. Kinderh.*, Stuttg., 1910, lii. 46.	—	3¾ m.	„	Human milk	7685	3	—	0·047	0·023
Cronheim und Müller	*Biochem. Zeitsch.*, Berlin, 1908, ix. 76.	Lo. (1)	4 m.	„	Milk + water + sugar	3890	4	6·1	0·22	0·044
„ „	„ „ „ „ „	Lo. (2)	4 m.	„	„ „	3983	4	7·06	0·22	0·042
„ „	„ „ „ „ „	Lo. (3)	4 m.	„	„ „	4092	4	7·48	0·22	0·020
„ „	„ „ „ „ „	Lo. (4)	4 m.	„	„ „	4129	4	6·90	0·22	0·058
„ „	„ „ „ „ „	Lo. (5)	4 m.	„	„ „	4186	4	6·47	0·22	0·029
„ „	„ „ „ „ „	Hu. (1)	4 m.	„	„ „	7897	4	11·36	0·18	0·002
„ „	„ „ „ „ „	Hu. (2)	4 m.	„	„ „	7997	4	10·75	0·18	0·028
„ „	„ „ „ „ „	Hu. (3)	4 m.	„	„ „	8157	4	11·77	0·18	0·020
„ „	„ „ „ „ „	Hu. (4)	4 m.	„	„ „	8300	4	11·62	0·18	0·018
„ „	„ „ „ „ „	Hu. (5)	4 m.	„	„ „	8453	4	12·17	0·16	0·005
„ „	*Jahrb. f. Kinderh.*, Leipz., 1909, lvii. 45	II (*a*)	4 m.	„	¾ milk + milk sugar	6918	4	—	0·18	0·059
„ „	„ „ „ „ „	II (*b*)	4 m.	„	„ „	6923	4	—	0·19	0·06
Blauberg	*Zeits. f. Biol.*, Münch. u. Leipz., 1900, xl. 36	(22)	5 m.	„	milk + water	6770	6	—	0·04	0·025
Rothberg	*Jahrb. f. Kinderh.*, Leipz., 1907, lxvi. 69	Halm	5½ m.	„	Skim milk + milk sugar	5195	3	—	0·26	0·039
Orgler	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 373	Max G. (1)	5½ m.	„	⅔ milk + ⅓ *Mehlsuppe* + 5 % sugar	6740	3	6·52	0·18	0·019
„	„ „ „ „ „	Max G. (2)	5½ m.	„	Same diet + 1 gr. calc. acet. p. d.	6825	3	9·2	0·20	−0·035
Cronheim und Müller	*Jahrb. f. Kinderh.*, Leipz., 1903, lvii. 45	I (*b*)	6 m.	„	¾ milk + milk sugar	6598	4	12·66	0·19	0·011
„ „	„ „ „ „ „	I (*a*)	6 m.	„	„ „	6597	4	12·66	0·19	0·03
Klotz	„ „ 1909, lxx. 1	G. K. (1)	6 m.	„	½ milk + ½ *Mehlsuppe* + malt	4200	3	7·52	0·18	0·014
„	„ „ „ „ „	G. K. (2)	6 m.	„	Soured milk	4200	3	6·42	0·16	0·05
Orgler	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 373	Kurt S. (1)	6½ m.	„	½ milk + ½ *Schleim* + 5 % sugar	3990	3	5·1	0·18	0·019
„	„ „ „ „ „	Kurt S. (2)	6½ m.	„	Same diet + 1 gr. calc. acet. p. d.	4075	3	8·45	0·25	−0·094
Klotz	*Jahrb. f. Kinderh.*, Leipz., 1909, lxx. 1	H. W. (1)	7 m.	„	½ skim milk + ½ *Mehlsuppe* + malt	6580	3	9·4	0·11	0·008
„	„ „ „ „ „	H. W. (2)	7 m.	„	Soured milk	6500	3	6·0	0·13	0·008
Bruck	*Monats. f. Kinderh.*, Leipz. u. Wien, 1908, vi. 570	—	8½ m.	„	— —	5600	—	—	0·13	0·05
Birk	„ „ 1908, vii. 450	Sch. (1)	9 m.	„	½ milk + ½ *Mehlsuppe* + 40 gr. malt sugar	5640	3	6·9	0·12	0·056

APPENDIX III (*continued*)

Author.	Reference.	Name.	Age.	Condition.	Diet.	Average Wt.	Duration of Experiment.	Average Daily Wt. of Dried Faeces.	Average Daily CaO Intake per Kilo Body Wt.	Average Daily CaO Retention per Kilo Body Wt.
Birk	*Monats. f. Kinderh.*, Leipz. u. Wien, 1908, vii. 450	Sch. (2)	9 m.	Healthy	Same diet + cod oil + phosph. oil	5650	3	8·2	0·16	0·071
Klotz	*Jahrb. f. Kinderh.*, Leipz., 1909, lxx. 1	— (1)	9 m.	,,	½ milk + *Mehlsuppe* + 60 gr. malt	6720	3	7·7	0·1	0·005
,,	,, ,, ,, ,,	— (2)	9 m.	,,	,, ,,	6745	3	6·0	0·09	0·004
,,	,, ,, ,, ,,	— (3)	9 m.	,,	,, ,,	6745	3	4·13	0·08	0·007
Meyer	*Biochem. Zeits.*, Berlin, 1908, xii. 422	B. (1)	10 m.	,,	⅔ milk + ⅓ *Schleim* + sugar	8820	4	2·70	0·15	0·012
,,	,, ,, ,, ,,	B. (2)	10 m.	,,	,, ,,	8820	4	4·46	—	−0·0002
Birk	*Monats. f. Kinderh.*, Leipz. u. Wien, 1908, vii. 450	K. (1)	10½ m.	,,	½ milk + ½ *Mehlsuppe* + 40 gr. malt sugar	5990	3	7·3	0·14	0·03
,,	,, ,, ,, ,,	K. (2)	10½ m.	,,	Same diet + cod oil + phosph. oil	6040	3	11·8	0·13	0·032
Ahlqvist	*Studien über den Stoffwechsel, Skand. Arch. f. Physiol.*, Leipz., 1916, xxxiv. 1	Erik I	3 y. 6 m.	,,	Mixed diet	12·400	7	17·232	0·1074	0·0301
,,	,, ,, ,, ,,	Erik II	3 y. 6 m.	,,	,, ,,	12·400	7	15·365	0·1172	0·0338
,,	,, ,, ,, ,,	Eino	6 y. 1 m.	,,	,, ,,	19·400	7	20·781	0·1183	0·0361
,,	,, ,, ,, ,,	Wilhelm I	9 y. 8 m.	,,	,, ,,	25·200	7	31·735	0·1324	0·0588
,,	,, ,, ,, ,,	Wilhelm II	9 y. 8 m.	,,	,, ,,	25·500	7	28·714	0·1173	0·0442
,,	,, ,, ,, ,,	Gunner I	3 y. 9 m.	Lupus	,, ,,	14·500	7	13·393	0·1345	0·0467
,,	,, ,, ,, ,,	Gunner II	3 y. 9 m.	,,	,, ,,	14·500	7	13·863	0·1580	0·0575
,,	,, ,, ,, ,,	2. Radolph	4 y. 3 m.	Scrofula	,, ,,	14·700	7	10·221	0·1201	0·0539
,,	,, ,, ,, ,,	5. Ármas	4 y. 7 m.	Tuberculosis	,, ,,	14·700	7	12·655	0·1664	0·0735
,,	,, ,, ,, ,,	Swen I	5 y.	Scrofula	,, ,,	15·500	7	14·102	0·0941	0·0192
,,	,, ,, ,, ,,	Swen II	5 y.	,,	,, ,,	15·600	7	18·681	0·1032	0·0347
,,	,, ,, ,, ,,	Rudolp I	5 y. 1 m.	,,	,, ,,	15·800	7	14·753	0·1017	0·0313
,,	,, ,, ,, ,,	Rudolp II	5 y. 1 m.	,,	,, ,,	15·500	7	18·480	0·0997	0·0343
,,	,, ,, ,, ,,	1. Lauri	6 y. 6 m.	,,	,, ,,	18·300	7	12·455	0·1003	0·0485
,,	,, ,, ,, ,,	4. Kalle	6 y. 6 m.	,,	,, ,,	18·900	7	14·422	0·0874	0·0313
,,	,, ,, ,, ,,	Lauri I	7 y. 2 m.	,,	,, ,,	18·100	7	20·332	0·1288	0·0319
,,	,, ,, ,, ,,	Lauri II	7 y. 2 m.	,,	,, ,,	18·100	7	22·793	0·1492	0·0367

,,	,, ,, ,, ,,	6. Gustaf	8 y. 5 m.	Tuber-culosis	,, ,,	22·400	7	19·294	0·1464	0·0645
,,	,, ,, ,, ,,	3. Arthur	8 y. 11 m.	Scrofula	,, ,,	25·200	7	15·240	0·0715	0·0294
,,	,, ,, ,, ,,	Bertel I	9 y. 1 m.	Tuber-culosis	,, ,,	23·000	7	18·276	0·1081	0·0271
,,	,, ,, ,, ,,	Bertel II	9 y. 1 m.	,,	,, ,,	22·700	7	16·605	0·1101	0·0169
Birk und Orgler	*Monats. f. Kinderh.*, Leipz. u. Wien, 1910, ix. 544	I	1¼ m.	Cranio-tabes	Milk + water + 5 % *Sorhlet nahrsucker*	2200	5	5·39	0·2	−0·08
,, ,,	,, ,, ,, ,,	II	2½ m.	,,	,, ,,	2900	5	4·29	0·2	0·027
,, ,,	,, ,, ,, ,,	III	4½ m.	,,	Human milk	3440	3	3·76	0·06	0·021
Rothberg	*Jahrb. f. Kinderh.*, Leipz., 1907, lxvi. 6	Saessner (*a*)	4 m.	Rickets	Skim milk	3800	3	—	0·22	0·027
,,	,, ,, ,, ,,	Saessner (*b*)	4½ m.	,,	½ milk + ½ *Mehl-suppe* + malt	3950	3	—	0·11	−0·013
Orgler	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 373	Kurt M. (3)	4½ m.	,,	Human milk	3460	3	3·76	0·06	0·020
,,	,, ,, ,, ,,	Kurt M. (4)	4½ m.	,,	Human milk + 2 gr. calc. acet. p. a.	3510	3	—	0·2	0·022
Schabad	*Arch. f. Kinderh.*, Stuttg., 1910, liii. 380	Nickolojew (*a*)	5 m.	,,	Human milk	5870	3	*11·8	0·05	0·026
,,	,, ,, ,, ,,	Ivanow	5 m.	,,	Milk + rice-water	4330	7	*17·7	0·22	0·02
Cronheim und Müller	*Biochem. Zeitsch.*, Berlin, 1908, ix. 76	Bi. (1)	6 m.	,,	Milk + water + milk sugar	4121	4	5·6	0·22	0·082
,, ,,	,, ,, ,, ,,	Bi. (2)	6 m.	,,	,, ,,	4145	4	7·0	0·22	0·032
,, ,,	,, ,, ,, ,,	Bi. (3)	6 m.	,,	,, ,,	4172	4	4·56	0·21	0·064
,, ,,	,, ,, ,, ,,	Bi. (4)	6 m.	,,	,, ,,	4171	4	5·1	0·19	0·073
,, ,,	,, ,, ,, ,,	Bi. (5)	6 m.	,,	,, ,,	4189	4	5·0	0·21	0·046
Arndt	Quoted by Schabad in *Arch. f. Kinderh.*, Stuttg., 1910, liii. 380	— (1)	6 m.	,,	*Malzsuppe*	3620	5	—	0·13	−0·002
,,	,, ,, ,, ,,	— (2)	6 m.	,,	Milk, malt, *Mehl*	3680	5	—	0·13	−0·029
Schabad	,, ,, ,, ,,	Nicholojew (*b*)	6 m.	,,	Human milk	6410	5	*8·0	0·05	0·013
Orgler	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 373	Erich W. (1)	6½ m.	,,	⅔ milk + ⅓ *Mehl-suppe* + 5 % sugar	6011	2	5·32	0·17	0·044
,,	,, ,, ,, ,,	Erich W. (2)	6½ m.	,,	Same diet + 1 gr. calc. acet. p. d.	5950	3	7·5	0·2	0·061
Dibbelt	*Die Pathogenese der Rachitis*	S.	7 m.	,,	Buttermilk	4800	—	—	0·23	−0·07
Orgler	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 373	Walter H. (1)	7½ m.	,,	½ milk + ½ *Mehl-suppe* + 4 % malt extract	5730	3	14·15	0·12	−0·096
,,	,, ,, , ,,	Walter H. (2)	7½ m.	,,	Same diet + 1 gr. calc. acet.	5730	3	9·9	0·18	0·009

* Faeces weighed before drying.

APPENDIX III (*continued*)

Author.	Reference.	Name.	Age.	Condition.	Diet	Average Wt.	Duration of Experiment.	Average Daily Wt. of Dried Faeces.	Average Daily CaO Intake per Kilo Body Wt.	Average Daily CaO Retention per Kilo Body Wt.
Birk	*Monats. f. Kinderh.*, 1908, vii. 450	T. (1)	8 m.	Rickets	½ milk + ½ *Haferschleim* + milk sugar	4050	3	5·7	0·11	0·002
,,	,, ,, ,, ,,	T. (2)	8 m.	,,	Same diet + cod-oil and phosph. oil	4050	3	4·7	0·1	0·01
,,	,, ,, ,, ,,	F. (1)	8 m.	,,	½ milk + ½ *Haferschleim* + milk sugar	5740	3	5·6	0·1	−0·008
,,	,, ,, ,, ,,	F. (2)	8 m.	,,	Same diet + cod-oil and phosph. oil	5840	3	5·4	0·09	0·006
Schabad	*Arch. f. Kinderh.*, Stuttg., 1910, liii. 380	A. Ivanow	8½ m.	,,	Milk and rice *Schleim*	7250	3	*40·8	0·1	0·013
Rothberg	*Jahrb. f. Kinderh.*, Leipz., 1907, lxvi. 6	Buchwald	9 m.	,,	⅔ milk + ⅓ water + milk sugar	6000	3	—	1·12	0·004
Klotz	,, ,, 1909, lxx. 1	W. B. (*a*)	9½ m.	,,	½ milk + *Mehlsuppe* + malt extract	4385	3	9·92	0·14	−0·012
,,	,, ,, ,, ,,	W. B. (*b*)	9½ m.	,,	½ milk + *Mehlsuppe* + 1·5 gr. lactic acid	4345	3	5·5	0·16	0·03
,,	,, ,, ,, ,,	W. B. (*c*)	9½ m.	,,	½ milk + *Mehlsuppe* + 4·0 gr. lactic acid	4370	3	4·65	0·17	0·02
,,	,, ,, ,, ,,	W. B. (*d*)	9½ m.	,,	½ milk + *Mehlsuppe* + 8·0 gr. lactic acid	4350	3	5·97	0·14	−0·003
Schabad	*Arch. f. Kinderh.*, Stuttg., 1910, liii. 380	Sampron	11 m.	,,	Human milk	7550	3	*8·83	0·02	−0·013
Cronheim und Müller	*Biochem. Zeitsch.*, Berlin, 1908, ix. 76	Ja. (3)	11 m.	,,	Milk + water + milk sugar	6211	4	13·55	0·22	0·007
,, ,,	,, ,, ,, ,,	Ja. (4)	11 m.	,,	,, ,,	6363	4	9·92	0·22	0·020
,, ,,	,, ,, ,, ,,	Ja. (5)	11 m.	,,	,, ,,	6478	4	9·45	0·21	0·047
Schabad und Sorochowitsch	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 12	S. S.	1 y.	,,	Milk and bread	5640	5	—	0·16	0·038
Orgler	,, ,, ,, x. 373	Kurt St. (1)	1 y. 1 m.	,,	Full milk	6640	4	11·84	0·19	−0·040
,,	,, ,, ,, ,,	Kurt St. (2)	1 y. 1 m.	,,	½ milk + ½ *Mehlsuppe* + 3 % sugar	6530	4	5·6	0·11	0·006

,,	,, ,, ,, ,,	Kurt St. (3)	1 y. 1 m.	,,	Same diet + 2 gr. calc. phos. p. d.	6450	4	5·69	0·17	0·007
Schabad	*Arch. f. Kinderh.*, Stuttg., 1910, liii. 380	Michaelow	1 y. 1½ m.	,,	Human milk	7690	3	*16·47	0·03	−0·008
,,	,, ,, ,, ,,	Sjedow	1 y. 5 m.	,,	Bread and milk	7000	3	*28·0	0·12	0·034
,,	,, ,, ,, ,,	Rjabzow	1 y. 6 m.	,,	,, ,,	6900	7	*16·14	0·23	0·059
Klotz	*Jahrb. f. Kinderh.*, Leipz., 1909, lxx. 1	Sch. (1)	1 y. 6 m.	,,	Buttermilk	4425	3	9·4	0·22	−0·11
,,	,, ,, ,, ,,	Sch. (2)	1 y. 6 m.	,,	Soured skim milk	4460	3	5·9	0·18	−0·11
Schabad	*Arch. f. Kinderh.*, 1910, liii. 380	Hanow (1)	1 y. 7 m.	,,	Bread and milk	8860	14	*25·86	0·13	0·019
,,	,, ,, ,, ,,	Hanow (2)	1 y. 7 m.	,,	,, ,,	9750	7	*29·93	0·11	0·016
,,	*Zeits. f. Klin. Med.*, Berlin, 1910, lxix. 435	Timphiewa	1 y. 9 m.	,,	,, ,,	7300	7	*19·43	0·19	0·016
Schabad und Sorochowitsch	*Monats. f. Kinderh.*, Leipz. u. Wien, 1911, x. 12	Besminow	1 y. 11 m.	,,	,, ,,	7330	6	*17·16	0·17	0·1
Schabad	*Zeits. f. Klin. Med.*, Berlin, 1909, lxvii. 454	Tarakanow	2 y. 4 m.	,,	,, ,,	8000	3	*57·5	0·22	0·06
,,	,, ,, ,, ,,	Weissiliew	2 y. 6 m.	,,	,, ,,	8100	7	*26·34	0·16	0·025
,,	*Arch. f. Kinderh.*, Stuttg., 1910, liii. 380	Klementjew	3 y. 6 m.	Convalescent Rickets	,, ,,	11800	3	*15·6	0·2	0·06
,,	,, ,, ,, ,,	XV	4 y.	Rickets	Tea, milk, bread	11700	14	—	0·04	−0·002
,,	,, ,, ,, ,,	XVI	4 y.	,,	Bread and milk	11750	14	—	0·04	0·02
,,	,, ,, ,, ,,	IX	4 y.	,,	,, ,,	10820	14	—	0·1	0·01
,,	,, ,, ,, ,,	Borodina	8 y.	Convalescent Rickets	Tea, milk, bread	19450	7	*21·87	0·08	0·042

* Faeces weighed before drying.

Appendix IV.

Clinical Notes.

I. *Normal Cases.*

Case No. 1. B. H., aged 8¾ months. Absolutely normal infant.

Case No. 2. J. A. B., aged 6 months. An absolutely normal infant who had a birth weight of 6½ lb., and on admission a weight of 16 lb. 3 oz. He had been fed on milk and water equal parts ℥vi, and ℥ss. Virol every three hours.

Case No. 3. A. B., aged 2½ years, admitted to hospital with primary broncho-pneumonia, otherwise a normal child. Crisis occurred four days after admission, and metabolism experiment was carried out sixteen days later over a period of three days.

Case No. 4. C. B., aged 4 years. Admitted to hospital with chorea and V.D.H. Metabolism experiment carried out after ten weeks' residence when all active manifestations had disappeared.

Case No. 5. R. D., aged 8 years. One week convalescent from lobar pneumonia.

Case No. 6. J. L., aged 9½ years. Absolutely normal child. Admitted to hospital with history of thirst, but observation over a period of three weeks failed to reveal anything abnormal.

Case No. 7. J. A., aged 9½ years. Admitted to hospital as case of epilepsy of three months' duration. Was resident in hospital one month and had only one slight fit one week after admission. Metabolism experiment carried out just before dismissal. Seemed quite a healthy child otherwise.

Case No. 8. D. J., aged 10 years. Admitted to hospital with rheumatic arthritis and endocarditis. Metabolism experiment carried out four weeks later when all active manifestations had disappeared.

II. *Cases of Rickets.*

Case No. 1. Boy, aged 8 months, admitted to hospital on account of irritability of five months' duration. He seemed absolutely healthy except for a questionable laryngismus stridulus heard on two occasions. He had two teeth, and physical examination was negative. This case was used as a control, the diet consisting of undiluted cows' milk ℥vii + ℥i sugar, 5x = 1 litre per day. He was sent home after the completion of the metabolism experiment, but was returned to the hospital four months later when he presented a most marked degree of rickets as evidenced by head sweating, epiphyseal enlargement, rosary and fiddle-shaped deformity of the chest.

Case No. 2. Girl, aged 14 months, admitted to hospital with rickets and broncho-pneumonia. The child had been breast-fed for three months, thereafter on undiluted milk and porridge, and from the age of 11 months on the general diet of the household. For three months she had been getting Virol (1 jar weekly). She had never cut any teeth, and had never been able to sit unsupported. At the time of coming under observation she presented a severe degree of rickets, square head with sutures patent and the anterior fontanelle widely open, a rosary, epiphyseal enlargement and curvature of the long bones of both upper and lower limbs.

There was generalized bronchitis with a patch of broncho-pneumonia. Fever continued for fourteen days after admission and five days later Olei Phos. ½ mm. Olei Morrhuae ʒi was administered thrice daily. Ten days still later a metabolism experiment was carried out over a period of one week on a purely milk diet. The child improved somewhat, especially after the institution of treatment by massage and electricity, but fifteen weeks after admission, i. e. eight weeks after the cessation of the metabolism experiment, she developed broncho-pneumonia and died.

Cases No. 3 and 4 refer to the same child, a girl, aged 14 months, admitted to hospital with broncho-pneumonia. She was a healthy child at birth; was breast-fed for six months; had whooping-cough at 8 months and measles at 10 months, but was said to be enjoying good health until nine days before admission, when cough, fever, and dyspnoea developed. On admission there was a definite broncho-pneumonia involving the right upper and middle, and left lower lobes. There was a severe degree of rickets, she had no teeth, the anterior fontanelle was unduly patent, the epiphyses were enlarged, and a rosary with fiddle-shaped chest was present. Fever subsided two days after admission, and the metabolism experiments were conducted three weeks later for two periods of three days each at an interval of two days. The diet during the first period consisted of undiluted milk, and during the second period of milk with bread and butter.

Cases No. 5 and 6 also refer to the same child, a boy aged 2 years, admitted on account of rickets. He had been breast-fed for six weeks, and thereafter on cows' milk in apparently sufficient quantity. He sat up at 1 year, cut his first tooth at 17 months, but had never walked. He was a markedly rachitic child with large head and overhanging forehead, anterior fontanelle one inch square, rosary and epiphyseal enlargement. The spleen was palpable. Blood examination gave the following: haemoglobin 74 per cent., red cells 3,940,000 and leuc. 10,400. The first experiment, on a pure milk diet was conducted from 29th May till 1st June, seven days after admission. Blood examination (4th June) for calcium gave 0·11 grm. per cent. Olei Morrhuae and Olei Phos. were commenced on 6th June, and the second metabolism experiment, on a diet of milk, bread and butter, was conducted from 9th till 12th June.

Case No. 7. Girl, aged 2 years, admitted to hospital on account of rickets. She was a healthy child at birth, was breast-fed for two months, and then on undiluted milk till nine months, and later on the 'run of the house'. She cut her first tooth at 6 months, sat up at 9 months, and walked at 1 year and 8 months, but from age of 1 year and 10 months had shown a progressive disinclination to walk, and at date of admission usually refused even to stand. On admission there was marked rickets, as evidenced by large head, open anterior fontanelle, rosary and epiphyseal enlargement. The metabolism experiment on a diet of three pints of milk daily was conducted for nine days. During this period there was a tendency to constipation, and liquid paraffin was administered to counteract it.

Case No. 8. Girl, aged 2 years and 7 months, admitted on account of rickets. She was healthy at birth, was breast-fed for one year, and then on milk, porridge, bread and soup. She cut her first tooth at 10 months and walked at 15 months, but during the last six months had 'gone off her feet'. The father was idle and the mother was working as a lamplighter, and in consequence the child was not taken much out of doors. The child was definitely rachitic, as evidenced by patent anterior fontanelle, rosary, fiddle-shaped chest, epiphyseal enlargement and curvature of bone tibiae.

Case No. 9. Girl, aged 15 months, admitted to hospital with marked rickets, as evidenced by open fontanelle, rosary, fiddle-shaped chest, epiphyseal enlargement, curvature of both femora, and profuse sweating. She was healthy at birth

and was breast-fed for eighteen months, cut her first tooth at 14 months, but had never walked. She had measles at 1 year, and whooping-cough at 14 months, but apparently made good recoveries. Two weeks after admission she received Olei Phos. and Olei Morrhuae, which were continued for six weeks, when a metabolism experiment of six days' duration on a diet of porridge and milk was carried out. At this date the rachitic condition had not apparently improved.

Case No. 10. Girl, aged 3 years, came under observation on account of her inability to walk. She was a healthy child at birth, was breast-fed for ten months, then on milk and porridge till 18 months, and thereafter on the general diet of the household. She cut her first tooth at 6 months, but never walked. She had scarlet fever at 19 months. At the time of examination she was unable to stand without support, and presented a severe degree of rickets in an open anterior fontanelle, rosary, fiddle-shaped chest, curvature of both clavicles and left fore-arm. There was a slight facial phenomenon, but there had never been noted carpo-pedal spasm or laryngismus stridulus. A metabolism experiment extending over three days was carried out on a diet of milk and bread and butter; the addition of bread and butter to the diet and the small quantity of milk accounts for the relatively small intake of calcium. Blood examination for calcium three days after cessation of metabolism experiment: 0·015 grm. per 100 c.c. whole blood.

Case No. 11. Boy, aged 4 years, came under observation on account of inability to walk. He was a healthy child at birth and had never been breast-fed. He was fed on cows' milk till 14 months, and thereafter on the general diet of the household. He had been resident in the hospital at the age of 2 years and 4 months, on account of rickets. He was unable to walk, but with massage and electricity improved, and was dismissed able to walk. He contracted pneumonia eight months ago, had been practically confined to house since then and had 'gone off his feet entirely'.

On admission he presented marked signs of rickets. The anterior fontanelle was not quite closed, the epiphyses were enlarged, there was a rosary with fiddle-shaped deformity of the chest, and he was quite unable to support himself in the erect posture.

Examination of blood, day after admission, gave following results:

Hb. 72 per cent.
Red cells, 5,120,000.
White cells, 11,200.
CaO per 100 c.c. whole blood 0·011 grm.

One week after admission a metabolism experiment was carried out on a diet of milk, bread and butter, which he had been having since admission, and extended over a period of three days. Seven days after cessation of experiment he developed measles and was removed to an isolation hospital.

Case No. 12. Girl, aged 7 years. Had always enjoyed good health till nine months prior to coming under observation, when she commenced to suffer from pains in the limbs and to be disinclined to play. These symptoms had gradually progressed. On admission to hospital there was definite rickets, as evidenced by rosary, epiphyseal enlargement, and X-ray changes at the ends of the long bones. She was never breast-fed, but had been given various dilutions of milk and water. She walked at 14 months, and until the present illness had presented no symptoms suggestive of rickets. She was one of a family of 15, of whom five had been rachitic.

A metabolism experiment extending over a period of three days and on a diet of milk, bread and butter, was carried out after she had been on this diet for three days. Examination of the blood one week later revealed 0·010 grm. of CaO per 100 c.c. whole blood. She was thereafter treated with Olei Morrhuae and

Olei Phos. and massage and electricity and left hospital much improved after two weeks' residence.

Case No. 13. Girl, aged 13 years, admitted to hospital on account of pains in the arms and legs of four months' duration.

She was a congenital syphilitic as evidenced by saddle nose, Hutchinson's teeth, interstitial keratitis and scarring round the mouth.

She was said to have been a healthy infant, and to have learned to walk at 2 years. She developed deafness after measles at the age of 6 years. Three years ago she suffered from 'sore eyes' and was practically blind for some time.

Four months ago she commenced to suffer from pains in her limbs, specially severe during the day. Examination revealed, in addition to the above manifestations of old syphilis, epiphyseal enlargement, and X-ray examination of the wrists showed the changes typical of late rickets, viz.: widening of the epiphyseal lines and deficiency of calcium at the lower ends of the diaphyses.

Immediately after admission a metabolism experiment, extending over four days, on a diet of milk, bread and butter, was carried out.

Examination of the blood immediately before the metabolism experiment gave CaO 10 mg. per 100 c.c. of whole blood.

The patient was dismissed I.S.Q. a few days later.

BLOOD VISCOSITY AND BLOOD-PRESSURE[1]

By D. MURRAY LYON
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Introductory.

In the healthy subject the blood viscosity is maintained at a fairly uniform level, and shows only a slight diurnal variation which depends on the intake of food and fluid. On the other hand, wide departures from the normal are found in many diseased conditions.

It has long been suspected that a close relationship might exist between blood viscosity and blood-pressure, and several authors (Müller and Inada (1), Robert-Tissot (2), Cheinisse (3), Clifford Allbutt (4)) have suggested, on theoretical grounds, that a thickening of the blood might increase the blood-pressure and play an important part in the production of vascular disease. Of those investigators who have examined the question, very few have found any relationship whatever between the viscosity of the blood and the blood-pressure. Bachmann (5) and Welsh (6) denied that any connexion existed. Bucco (7), Determann (8), and Trumpp (9) found some correspondence between the blood-pressure and the blood viscosity when these were abnormally high or low, but no relationship at all at the normal ranges. Blunschy (10) noted that during exertion the viscosity and the blood-pressure ran parallel, though here the connexion was probably purely accidental. Hess (11) attempted to solve the problem by producing an artificial plethora in animals. He gave repeated intravenous injections of saline, gelatine solutions, or blood, but at the end of two and a half months was unable to find any evidence of cardiac enlargement.

An interesting and valuable contribution to the subject was made by Martinet (12). As a result of a long series of observations on hospital patients, he classified his cases into three groups—(*a*) 'Les eusystoliques', those who had a blood-pressure corresponding to their blood viscosity; (*b*) 'Les hypersystoliques', where the blood-pressure was high but the viscosity low; and (*c*) 'Les hyposystoliques', where the pressure was diminished and the blood viscosity raised. Martinet is a strong advocate of the great importance of the blood viscosity in regulating the blood-pressure. Curiously enough he includes in his eusystolic

[1] A grant was made by the Moray Fund of the Edinburgh University towards the expenses of this work.

group not only normal cases, but anaemic patients with thin blood and a low blood-pressure, and also cases of 'plethora' which show a proportionate increase in both blood-pressure and viscosity.

The importance of the blood viscosity as a factor in maintaining blood-pressure has also been emphasized by Bayliss (13), who advocated the use of a 7 per cent. gum solution, in place of normal saline, in transfusion of severe haemorrhage cases.

The powers of the body to compensate for alterations of blood thickness must be very considerable, for little direct evidence of the influence of blood viscosity on blood-pressure has been found. In polycythaemia, for example, muscular hypertrophy would be expected in all the chambers of the heart, yet Parkes Weber (14) was unable to find it in several cases that he examined. This observation is in agreement with those of Hess (11) and of Bence (15), who have noted that hypertrophy of the heart may be absent in cases where the blood viscosity had been high for a long time.

Failure to discover a hyperviscous blood in cases of advanced arterial sclerosis does not prove that a heightened blood viscosity takes no part in the production of vascular disease. It is quite possible that if the cases were examined early enough in the 'presclerotic' stage some thickening of the blood might be found.

Physical Considerations.

It is a physical law that the force necessary to propel a fluid varies directly with the viscosity of the fluid. Hence, in absence of interfering conditions, blood viscosity and cardiac activity must move together. The heart's action would be increased as the blood thickened and would diminish as the fluid became more watery.

Again, in a 'schema' of rigid tubes where the driving force and the outlet remain unchanged, a thickening of the perfusing fluid leads to a reduced outflow, and at the same time causes a rise in lateral pressure in the tube. If similar conditions obtained in the vascular system, a hyperviscous blood would raise the blood-pressure, while dilution of the blood would cause a fall in pressure.

These suppositions demand that the vascular system remains passive and fails to react to the changed conditions. This is extremely unlikely, for the vessels are controlled by a very sensitive mechanism which responds to the slightest stimulus.

Leaving aside the influence of the arterial walls, the blood-pressure depends on three principal factors—the cardiac energy (force and rate), the blood viscosity, and the sphincter action of the peripheral channels. In health these factors interplay so as to maintain the pressure at an approximately constant level, an alteration in one calling forth a change in one or both of the others. If the balance is upset by a change in the blood viscosity, compensation is effected by altering the driving force or the peripheral resistance. Of these methods the latter is much

more economical. Besides this, it is naturally desirable to save the heart as much as possible. Hence, most of the strain of compensation will fall on the peripheral vessels. These will dilate to allow the more rapid passage of a viscous blood, and will contract to maintain the blood-pressure at its proper level when the blood is thin. An increase of only 20 per cent. in the diameter of a tube will augment the flow by 50 per cent., an amount sufficient to deal quite easily with most pathological changes in the blood viscosity. Leonard Hill (16) has pointed out that a slight excitation of the vasomotor nerves can change the amount of blood flowing to a part by 100 per cent. or more. It is seldom that the viscosity of the blood is altered to such an extent, and therefore compensation will easily be effected without a change in the blood-pressure being produced. The facts, however, are not so simple. It is probable that the capillary areas must also be considered. In the larger vessels an alteration in the thickness of the circulating fluids is of comparatively little moment, but in the smallest channels its influence is paramount, for the narrower the tubes the greater the effect of increased viscosity. The result then of a high viscosity will be a great increase of resistance in the capillary beds, which may negative the effect of arteriole dilatation, and call directly for an increase in the driving pressure. But here again a compensating mechanism exists. It has been pointed out by many observers, and lately by Krogh, that in the resting state many capillaries are collapsed and only a few are acting. This reserve may be eaten into, and extra channels may be opened to compensate for the increased resistance, but the difficulty will again appear when full action is called for.

Where the driving power of the circulation is imperfect a vicious circle exists. The sluggish flow in the capillary regions results in excessive exchange of gases and produces a high CO_2 content (cyanosis) and an increased viscosity of the blood. The raising of the blood viscosity still further slows the stream. These factors are sufficient to account for passive congestion without introducing the question of venous stasis.

Where the viscosity of the blood is reduced a constriction of the arterioles may be necessary to raise the blood-pressure in order to offer the necessary resistance to the heart, and to prevent the arterial system from being too readily emptied. But the blood-pressure so raised will be of no service to the tissue areas beyond, and it is much more likely that the adjustment takes place in the capillaries themselves.

Another relationship between blood viscosity and blood-pressure must be considered. The plasma, in virtue of its proteins (some 6–8 per cent. of the fluid), possesses an osmotic pressure of about 30 mm. Hg. Secretion of urine by the kidney is only possible when the capillary pressure in the glomeruli is sufficient to neutralize this and leave a small margin (Starling, 17). A hyperviscous blood may show an increase of plasma protein, and this will necessitate a rise of glomerular pressure and with it also a heightening of the general blood-pressure. On the other hand, the viscosity of the blood may be influenced by alterations of intravascular pressure.

Injections of adrenalin by raising the blood-pressure lead to increased transudation from the vessels, cause concentration of the blood, and increase its viscosity. These changes are of a temporary nature, but similar (local) concentration of the blood follows obstruction or occlusion of veins. Conversely, the rapid filling up of the circulation with fluid from the tissues after severe haemorrhage may be looked upon as a reduction of viscosity produced by fall in intravascular pressure (capillary or venous probably).

Methods.

In order to obtain information as to whether any relationship could be demonstrated to exist between the viscosity of the blood and the blood-pressure a large number of subjects have been examined. They include a series of 80 normal persons, and upwards of 400 patients suffering from a wide range of pathological conditions. Viscosity estimations were made with Determann's viscosimeter (18), using the blood from the lobe of the ear, arterialized by previously rubbing the part, and prevented from coagulating by the addition of a minute quantity of hirudin. In all cases simultaneous examinations of the number of erythrocytes and the amount of haemoglobin were also made.

'Blood-pressure' readings were recorded with a Martin's sphygmomanometer, care being taken to avoid conditions which might cause a temporary rise in pressure. It is to be noticed that the maximum readings obtained in this way do not give the systolic *intra-arterial* pressure.

Normal Cases.

When the figures obtained for normal cases are plotted out, as in the figure on p. 406, several striking facts appear.

TABLE I.

Variations in Viscosity, Blood-pressure, &c., due to Age.

Age.	Viscosity.	R. B. C. Millions.	Hb.	B. P.	B. P./V.
Under 10	4·78	4·65	86	106	22
10–19	4·88	4·62	88	110	22·5
20–29	5·12	4·66	90	122	23·8
30–39	5·73	4·98	94	125	21·8
40–49	5·39	4·81	92	138	25·6
50–59	5·33	4·69	88	149	27·9
60 and upwards	5·24	4·68	89	153	29·1

It will be seen that the blood viscosity rises steadily with increasing years till it reaches a maximum in the period 30–39 and thereafter falls slowly. This curve corresponds closely with those for the number of R. B. C. and the percentage of haemoglobin. On the other hand, the 'blood-pressure' figures show no maximum in middle life, but continue to increase throughout the later decades. There is, however, a close parallelism in the earlier years, and it would seem probable that

the increasing blood viscosity during this period plays some part in raising the blood-pressure. If this be so, then the viscosity should still continue to influence the pressure in later life, but this is not evident from the chart. The discrepancy between the curves—the continued rise of systolic blood-pressure in spite of a fall in blood viscosity—must be explained by an ever-increasing sclerosis of the vessel-wall, the factor of 'arterial resistance' which makes a clinical B. P. reading higher than the true intravascular pressure. (See Stevenson (19)). *A priori* it would be thought that the actual vascular pressure should fall in the later years of life as the bodily activity diminishes.

Pathological Cases.

The details derived from cases of disease have been examined in four ways: (*a*) by comparison of figures given by individual cases at various periods and under different conditions; (*b*) by comparison of cases arranged under increasing B. P. readings; (*c*) by comparison of cases arranged under viscosity readings; and (*d*) by arranging all the cases in groups according to whether they showed high, normal, or low readings of blood-pressure and blood viscosity.

(*a*) Repeated examination of individual subjects at long intervals and under varying conditions showed no close parallelism between blood-pressure and blood viscosity. A patient, aged 51, who had disease of both the aortic and the mitral valves gave a blood-pressure reading of 160 mm. Hg and a viscosity figure of 4·75. Two months later, on readmission to hospital in an oedematous condition, the values were B. P. 168, V. 4·50. Then, after he had rested in bed for a month and had greatly improved in his general condition, the B. P. was 165 and the viscosity had again risen to 4·75.

A case of arterio-sclerosis, aged 60, when examined at weekly intervals, showed blood-pressure readings of 200, 195, 210, while the corresponding viscosity figures were 4·75, 5·25, and 5·30.

On the whole the thickness of the blood is less liable to variation than the blood-pressure, and the viscosity readings may remain practically constant while the pressure rises.

A patient, convalescing after an operation for varicose veins, showed on different days, B. P. 142, V. 4·20; B. P. 130, V. 5·20; B. P. 112, V. 5·05.

Sometimes, however, the blood-pressure readings were more steady than those of the viscosity; e. g. on three occasions a patient who suffered from aortic disease had a B. P. of 140 mm. Hg, while the viscosity of the blood stood at 5·50, 4·95, and 5·10.

(*b*) *Comparison of B. P. readings.* Table II gives the figures obtained from patients in an ordinary medical ward. No special selection has been made, so the list contains cases of very widely different nature. The data have been arranged in order of increasing blood-pressures. An examination of this table will show that there is no steady rise in the average viscosity as the blood-pressures mount. At each level of blood-pressure a very wide range of viscosity

figures is found, and comparatively high viscosities are met with in some cases where the B. P. is quite low. It would be dangerous to draw deductions from such a table, but it will be noticed that the lowest viscosity readings are collected in the upper part of the list, where the blood-pressures were below 140 mm. Hg. No similar arrangement of the high viscosity figures is present.

TABLE II.

Blood-Pressure and Viscosity in Pathological Conditions.

No. of Cases.	B. P. mm. Hg.	Average Viscosity.	Range of Viscosity.
14	Under 100	4·36	1·82–6·10
46	100+	4·88	2·75–6·40
43	110+	5·21	3·25–7·75
37	120+	5·11	2·37–7·03
28	130+	4·80	2·30–10·90
29	140+	4·87	3·45–6·13
16	150+	5·38	4·37–7·05
12	160+	5·53	4·25–8·50
7	170+	5·18	4·25–6·25
7	180+	4·59	4·25–5·00
4	190+	4·80	3·88–5·52
8	200+	5·27	4·95–6·25

TABLE III.

Viscosity and Blood-Pressure.

(A) High Viscosities.

No. of Cases.	Viscosity.	Average B. P.	Range of B. P.
2	10	137	132–142
2	8 +	163	160–165
8	7 +	134	118–165
4	6·75+	123	110–162
4	6·50+	119	110–122
11	6·25+	126	110–160
21	6 +	132	100–200
28	5·75+	128	100–178

(B) Low Viscosities.

No. of Cases.	Viscosity.	Average B. P.	Range of B. P.
61	4·50–4·75	124	95–190
43	4·35+	132	95–185
20	4·00+	120	105–145
5	3·75+	125	118–140
5	3·50+	132	120–140
4	3·25+	122	117–145
4	2·50+	119	95–136
3	2·00+	118	92–135
1	1·82	95	95

(*c*) In Table No. III the figures have been arranged in order of decreasing viscosity readings. At normal levels (4·75–5·75) no agreement was evident, and the figures have been omitted. Most of the average B. P. readings in the high viscosity group are within normal limits, but a few of the cases show a raised blood-pressure, while others are distinctly low. A somewhat closer correspondence between the figures is apparent in the hypoviscous group (Table III B). Cases

with viscosity readings under 3·50 have blood-pressures distinctly lower than those where blood is slightly more viscous, and in no case is a thin blood associated with a maximum pressure above normal. The lowest figures in this series are all from cases of anaemia, while a little higher in the list occur some oedematous nephritics with somewhat greater blood-pressures.

TABLE IV.

Group 1.

B. P. + V. +

Cardio-vascular group — all with *marked cyanosis.*
Heart failure cases: valvular or myocardial.
Aneurysm.
Chronic bronchitis.

Group 2.

B. P. = V. +

Cardiac and arterial cases and cases of cerebral haemorrhage with slight cyanosis present.
Acute pleurisies.
Convalescent phthisis and bone tuberculosis cases.
Gall-stones, tabes, neurasthenia, and a few nephritis cases.

Group 3.

B. P. − V. +

Pulmonary group.
Malaeration of the blood.
Acute pneumonias.
Pleurisies with effusion.
Carcinoma of lungs.
Asthma.
Phthisis and non-pulmonary T. B.
Mitral stenosis with cyanosis.
Convalescent pernicious anaemias.

Group 4.

B. P. + V. =

Cardio-vascular and renal cases without cyanosis.
Cerebral haemorrhage.
Arterio-sclerosis and heart failure with some oedema.
Subacute and chronic nephritis cases.

Group 5.

B. P. = V. =

Besides normal cases contains many cases where cyanosis and oedema occur together and neutralize each other.

Group 6.

B. P. − V. =

Convalescent pneumonias.
Convalescent pericarditis.
Pleurisy with effusion.
Mild cases of mitral stenosis.

Group 7.

B. P. + V. −

Hydraemia.
Acute nephritis with oedema.
Aortic stenosis, Mitral incompetence, Aneurysm, Arterio-sclerosis — with no cyanosis but showing some oedema.

Group 8.

B. P. = V. −

Many oedematous nephritics.
Some pernicious and other anaemias.

Group 9.

B. P. − V. −

Anaemias, both pernicious and others.
A few nephritis cases with some slight oedema.

(*d*) *Cases arranged according to both B. P. and V. readings.* When the variation of systolic blood-pressure in health is taken as 110–145, and the normal range of the blood viscosity as 4·70–5·70, the pathological cases naturally fall into nine groups. This arrangement, which is seen in Table IV, reveals some interesting facts.

The first striking thing is that, in spite of the wide range of diseases represented, cases of similar type tend to occur together in the same groups. Four of the divisions have distinctive characters. The other five groups occupy inter-

mediate positions between these extremes, and it will be noticed that in each of these groups either the pressure or the viscosity is normal. The prominent sections might be labelled—(1) Cyanosis, (3) Pulmonary insufficiency, (7) Hydraemia, and (9) Anaemia.

Of these four groups, two (Nos. 1 and 9) might be taken as proving a close relationship between the blood-pressure and the thickness of the blood, while the other two (Nos. 3 and 7) at first sight seem to contradict this. A high viscosity in one class of case is associated with a raised blood-pressure, and in another with a low pressure, and similarly, at one time a hypoviscous blood accompanies a high pressure, and at another time a low pressure. Can this apparent anomaly be explained?

The cases in Group 1 are all cardio-vascular, and showed the presence of a considerable degree of cyanosis. The primary fault in these cases is a failure in the driving force of the circulation combined with overfilling of the veins and relative stagnation of the blood. Movement in the capillary areas is much too slow, gaseous exchanges between the blood and the tissues proceed too far, and this leads to the production of cyanosis of peripheral origin. The increased amount of acid now present in the blood causes the red blood-corpuscles to swell at the expense of the plasma (20), and this raises the blood viscosity. Thus arises a vicious circle-heart failure, increased blood viscosity, and further embarrassment of the heart. We have seen that the easiest way by which the body can compensate for an increased thickness of the blood is by a dilatation of the peripheral channels. In cases of cardiac failure, however, this method is impossible, for the venous lakes and the capillary beds are already distended to their utmost. Nor can the blood-pressure be reduced by lessening the heart's action. Hence, since the body is unable to counteract the increased thickness of the blood, it directly leads to an increase in the blood-pressure in these cases.

No. 3. If the intra-arterial pressure depended entirely or principally on the thickness of the blood, it would be expected that all cases showing hyperviscous blood should also show a high B. P. This, however, does not occur, for some hyperviscous cases have a normal blood-pressure (Group 2), while others show a pressure abnormally low. How do these patients differ from those in Group 1? The majority of the cases in this section are pulmonary lesions. Here, as in Group 1, the blood viscosity is increased because of an alteration in the gas content of the fluid. The fault this time lies in the lungs, where oxygenation of the blood is imperfectly accomplished, and a cyanosis of central origin is produced. The increased viscosity of the blood that results from this must tend to embarrass the circulation, but in these cases ample compensation is possible. There is no distal stasis or oedema, and the capillary beds can be quite readily dilated so that the pressure does not increase, in spite of the enhanced thickness of the blood. The fact that in this group of patients the B. P. is actually below normal might be explained by dilatation of the distal vessels (the febrile flush of the skin, &c.) or by some weakening of the heart's action.

It is interesting to notice that cases of mitral stenosis are separated from all

other types of cardiac lesion by having a low blood-pressure. The high viscosity depends on the presence of some polycythaemia, and also of some cyanosis in the more severe cases. The low blood-pressure is due to the small volume of blood that is driven into the aorta at each systole by the atrophied and feeble ventricle. Probably the appearance of cases of non-pulmonary tuberculosis in this group is to be accounted for by the presence of some toxin which weakens the heart, while the viscosity is raised by some increased acidity of the blood.

In Group 9 we have a combination that is to be expected, a low arterial pressure accompanying a great weakening of the blood. The cases present are all anaemias of one kind or another, and include examples of chlorosis, pernicious anaemia, and various types of secondary anaemia. The blood in these cases is so thin that it flows too quickly and too easily through the vessels, and can contribute very little to the maintenance of the blood-pressure. Apparently peripheral constriction of the capillary beds is insufficient to cope with this, or more likely this method of compensation is not attempted since it would endanger the food supply of the tissues. A reduction in the cross-section of the capillaries would diminish the surface available for gas and food exchange, and these processes would also be cut down by the increased speed with which the blood would flow through the narrow tubes.

It is not suggested that the low blood-pressure in these cases depends entirely on the watery blood. Other factors must also be at work. Poor oxygenation and partial starvation of the tissues will lower the vascular tone and enfeeble the cardiac muscle. The importance of the thinness of the blood becomes evident when it is considered that in cases of anaemia there is a grave danger of the mean arterial pressure falling too low on account of the extremely ready flow and the absence of a proper resistance. This is to some extent prevented by increasing the rate of the heart, a symptom which is constantly found in anaemias.

It is interesting to notice that anaemias having a low blood-pressure corresponding with their low viscosity are classified by Martinet along with his 'eusystoliques'.

An apparently anomalous combination is found in Group 7, where cases show a high blood-pressure in spite of a diminished blood viscosity. The blood in many of these cases was just as thin as in the anaemias, and yet the result is different.

The usual explanation given for a heightened B. P. in cases of nephritis is that the damage to the kidney causes retention of some metabolite which has a pressor action. This may be true for some nephritics, but another explanation can be offered. The accumulation of fluids in the tissues in cases of renal dropsy must compress and empty the capillaries, much in the same way that the smaller vessels are affected in cloudy swelling. This closing of the peripheral blood channels would lead mechanically to a raising of blood-pressure in the arterial system, and such an increase would also be called for to endeavour to overcome the obstruction.

Still another factor must be considered. It is admitted that in the oedema-

tous stages of nephritis the blood itself becomes diluted and is also increased in total volume. This hydraemic plethora would increase the 'fullness' of the vascular system, the extra amount of fluid finding accommodation on the venous side of the circulation. Here we have another cause of the raised blood-pressure.

It is difficult to account for the presence of cases of heart failure in this group unless it is conceded that in them, as in the nephritics, a dilution of the blood accompanies the obvious tissue oedema. There was no question of a concurrent insufficiency of the kidneys in these cases, and no trace of cyanosis was present.

An examination of Table IV will show that cases of nephritis appear in several of the groups. Acute cases with great oedema and hydraemia fall into Group 7, while a few early cases with less oedema and some true anaemias occur in Groups 8 and 9. Subacute and chronic examples of renal disease are mostly found in Group 4, where a high blood-pressure is associated with a normal blood viscosity, but only a few nephritic patients have a definitely raised viscosity.

Conclusions.

1. In health a close parallelism can be demonstrated to exist between the increase of blood-pressure and blood viscosity up to middle life, but after this the agreement ceases. The viscosity readings then fall in keeping with the values of the R. B. C. and the Hb., while the B. P. figures continue to rise as the vessel-walls become more resistant to compression.

2. In disease the relationship is much less evident, a fact which is to be explained by the enormous power of compensation that the body possesses. When individual cases are followed over a period the figures seem to vary most capriciously. Comparison of the viscosity readings in a table arranged under increasing values of B. P. shows at each level of pressure a wide range of viscosity figures, while a little correspondence appears to exist at the extremes of the table.

A similar table arranged in values of viscosity gives no better results.

3. When all the pathological cases examined are arranged in nine groups according to the combination of B. P. and V. readings shown by them, some curious facts are evident. There is a tendency for cases of a similar nature to fall into the same group.

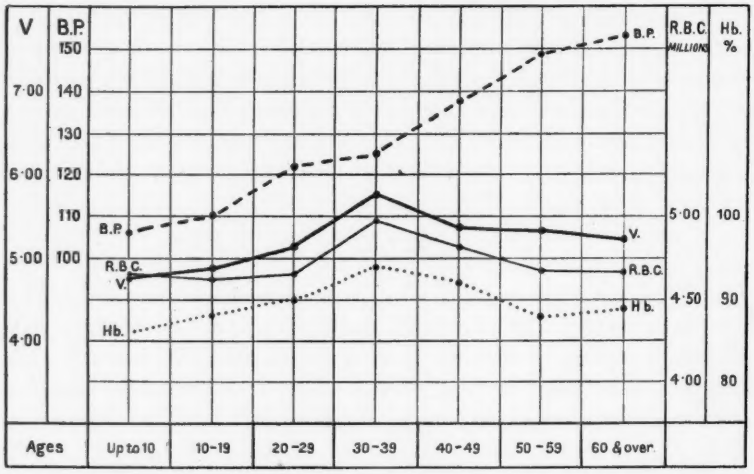
Four of the groups are prominent, containing respectively cases of cyanosis, malaeration of the blood, hydraemia, and anaemia.

4. It has been shown that in the patients with anaemia or cyanosis the alteration in the B. P. is very largely dependent on the thinness and thickness of the blood, since the normal mechanism of compensation cannot be brought into action.

5. In the two apparently anomalous groups where a low B. P. is associated with a raised V. and a high B. P. with a low V. the altered viscosity has been easily compensated for, and the unexpected B. P. value depends on other factors.

6. It has been suggested by a study of this material that the chief regulating mechanism in the circulation lies not in the arterioles but in the capillary areas.

7. It is concluded that the viscosity of the blood is a very important factor in maintaining the blood-pressure, but that alterations in the thickness of the blood can be easily compensated for by the body, and hence only in exceptional cases (anaemia and chronic venous congestion with cyanosis) does this control show itself in an altered blood-pressure.



Relation of blood viscosity to blood-pressure, red blood-corpuscles, and haemoglobin in healthy subjects at different age periods.

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